Background

In the general population, thrombotic events may occur as a result of changes in the balance of the hemostatic system, genetic abnormalities, or the presence of predisposing risk factors such as pregnancy, oral contraceptive/hormone replacement therapy, malignancy, obesity, and surgery, among others.[1]

Thrombus formation is a complex physiological phenomenon that serves as an appropriate response to vessel wall injury. It is a dynamic process that results when procoagulation activation overcomes the natural anticoagulant mechanisms and fibrinolytic system.[2] The three key factors contributing to hypercoagulability are endothelial damage (abnormal vessel wall), abnormal flow (blood stasis or turbulence), and altered coagulability (abnormal blood components). Any of these three factors may lead to pathological coagulation.

Prescribing Information

Thromboembolism Associated with HEMLIBRA and aPCC

Thrombotic events were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In clinical trials, thrombotic events were reported in 0.5% of patients (2/391) and in 5.4% of patients (2/37) who received at least one dose of aPCC.

No thrombotic event required anticoagulation therapy. Evidence of improvement or resolution was seen within one month following discontinuation of aPCC. One patient resumed HEMLIBRA following resolution of thrombotic event.

Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Monitor for the development of thromboembolism when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms, imaging, or laboratory findings consistent with thromboembolism occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of thrombotic events on a case-by-case basis.

Report an Adverse Event

You may report adverse events to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report adverse events to Genentech at (888) 835-2555.

Thrombotic cases in emicizumab-kxwh clinical trials, expanded access, compassionate use, and the postmarketing setting[3,4]

Clinical Trials, Expanded Access, and Compassionate Use:
Following an assessment of thrombotic microangiopathy (TMA) and serious thrombotic adverse events in the clinical development program, guidance and instructions were developed as part of a detailed risk mitigation strategy, and investigators were informed about the risk of thrombotic complications in October 2016.[3] The guidance developed includes instructions on the use and dosing of bypassing agents (BPAs) in combination with emicizumab-kxwh, as well as recommended medical supervision and laboratory monitoring after the administration of BPAs. These guidelines were implemented in all protocols and informed consent forms across all emicizumab-kxwh studies.

Postmarketing (*Initial FDA approval November 2017*):
Refer to the emicizumab-kxwh Prescribing Information for FDA-approved information on thromboembolism associated with emicizumab-kxwh and activated prothrombin complex concentrate (aPCC).

Thrombotic Cases Reported/Verified at Data Cutoff of June 30, 2020[3,4]

Cases from Clinical Trials, Expanded Access, and Compassionate Use

Cases	Cases with concomitant aPCC use exceeding the cumulative amount in the Boxed Warning†	Other Thrombotic Cases*	Clinical Trial Where Events Occurred
n=4	2	2	HAVEN 1 and 3, STASEY (Australia, Europe, North America)

Cases from the Postmarketing Setting

Cases	Cases with concomitant aPCC use exceeding the cumulative amount in the Boxed Warning†	Other Thrombotic Cases*	Locations of Cases
n=19	0	19	Asia, Australia, Europe, North America

* Thromboembolic events reported in patients, and reports may have included concomitant use of other hemophilia medications, including aPCC use not exceeding the cumulative dose in the Boxed Warning, or emicizumab-kxwh use alone.

† Per HEMLIBRA Prescribing Information, cases of TMA and serious thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving emicizumab-kxwh. Among pooled clinical trials (Phase 1/2, HAVEN 1, 2, 3, and 4), 13/130 (10%) instances of aPCC treatment consisted of on average a cumulative amount of >100 U/kg/24 hours of aPCC for 24 hours or more; 2 of 13 were associated with serious thrombotic events, and 3 of 13 were associated with TMA. No TMA or serious thrombotic events were associated with the remaining instances of aPCC treatment.

Patient safety is of the highest importance to us. We take all reports of safety events very seriously and encourage anyone who knows of an adverse event in a patient on emicizumab-kxwh to report the event to Genentech/Roche. We have systems and processes in place to collect, analyze, and monitor adverse events and report events to the FDA per regulations.

Due to the voluntary nature of postmarketing spontaneous adverse event reports, information may be missing or incomplete. Genentech/Roche has limited ability to ascertain and verify information from these adverse event reports, and reporters, including healthcare providers, are not obligated to share these details with Genentech/Roche. Furthermore, reporters themselves may not have access to all of the information regarding a patient's care for these events. Genentech/Roche does not provide additional details related to adverse events reported in the postmarketing setting, because the level of detail available and Genentech/Roche's ability to confirm individual details is variable. In addition, patient privacy is very important to Genentech/Roche, therefore we are careful not to disclose specific details about an adverse event that could jeopardize the privacy of either the patient or their family, or breach patient confidentiality. As a result of the variable level of detail in such spontaneously reported data, Genentech/Roche will provide information on the number of verified thrombosis reports on this website without assessments of relatedness or additional reported details related to events.

If any adverse event in a person taking emicizumab-kxwh impacts the overall benefit/risk profile of the medicine, we will share this information as quickly as possible and in accordance with any FDA requirements.

References
1. Cross M et al. *Seminars in Arthroplasty.* 2009;20:210-216; 2. Tripodi A et al. *J Thromb Haemost*. 2009;7:906-907; 3. Data on file. Genentech, Inc. June 2020; 4. Oldenburg J et al. *N Engl J Med*. 2017;377:809-818.

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