Background

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.[1] 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.

Thrombotic cases in emicizumab-kxwh clinical trials, expanded access, compassionate use, and the postmarketing setting[2,3]

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.[2] 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 at Data Cutoff of October 22, 2018[2,3]

Cases from Clinical Trials, Expanded Access, and Compassionate Use

Cases (n=2)	Proximity to BPA Dosing Guidance Introduction (October 2016)*	On average a cumulative amount of >100 U/kg/24h of aPCC for 24h or more†	Clinical Trial Where Event Occurred
Thrombotic case 1	Before	Yes	HAVEN 1
Thrombotic case 2	Before	Yes	HAVEN 1

Cases from the Postmarketing Setting

Cases (n=0)	On average a cumulative amount of >100 U/kg/24h of aPCC for 24h or more†
0 cases	Not applicable

- *Revised guidance on the use and dosing of BPA in combination with emicizumab-kxwh was implemented October 2016. Before/After=event occurred prior to/after implementation of BPA guidance in all protocols across all emicizumab-kxwh studies.
- †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 of more to patients receiving emicizumab-kxwh. Among pooled clinical trials (Phase 1/2, HAVEN 1, HAVEN 2, HAVEN 3, HAVEN 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.

- Among the 2 thrombotic cases that occurred in the HAVEN 1 clinical trial, 1 occurred in the US, and 1 occurred outside of the US (Ex-US).[2]

References

1. Tripodi A et al. J Thromb Haemost. 2009;7:906-907; 2. Data on file. Genentech, Inc. October 2018;
3. Oldenburg J et al. N Engl J Med. 2017;377:809-818.