Thrombotic microangiopathy comprises a heterogeneous group of disorders characterized by injured endothelial cells that are thickened, swollen, or detached, mainly from arterioles and capillaries. Pathological findings include vascular damage manifesting as arteriolar and capillary thrombosis, and characteristic abnormalities in the endothelium and vessel wall. Histologic and clinical features include schistocytes, microangiopathic hemolytic anemia, and thrombocytopenia, and organ injury.

Background

Cases of thrombotic microangiopathy (TMA) were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of activated factor IX complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In clinical trials, TMA was reported in 0.8% of patients (3/391) and in 8.1% of patients (3/37) who received at least one dose of aPCC. Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity.

Evidence of improvement was seen within one week following discontinuation of aPCC. One patient resumed HEMLIBRA following resolution of TMA. Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Monitor for the development of TMA when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of TMA on a case-by-case basis.

Prescribing Information

Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Cases from Clinical Trials, Expanded Access, and Compassionate Use

Cases from the Postmarketing Setting

TMA Cases Reported/Verified at Data Cutoff of June 30, 2020

Cases from Clinical Trials, Expanded Access, and Compassionate Use

Cases | Cases with concomitant aPCC use exceeding the cumulative amount in the Boxed Warning* | Clinical Trial Where Events Occurred
---|---|---
n=3 | 3 | HAVEN 1 (Australia, Europe, North America)

Cases from the Postmarketing Setting

Cases | Cases with concomitant aPCC use exceeding the cumulative amount in the Boxed Warning* | Locations of Cases
---|---|---
n=1 | 1 | North America

* 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.

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.

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 thrombotic microangiopathy 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