Background

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, thrombocytopenia, and organ injury.

Prescribing Information

Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Cases of thrombotic microangiopathy (TMA) 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, 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.

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 microangiopathy cases in emicizumab-kxwh clinical trials, expanded access, compassionate use, and the postmarketing setting

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. 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 TMA associated with emicizumab-kxwh and activated prothrombin complex concentrate (aPCC).

TMA Cases Reported/Verified at Data Cutoff of March 31, 2019

<table>
<thead>
<tr>
<th>Cases</th>
<th>Clinical Trial Where Events Occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=3</td>
<td>HAVEN 1 (Australia, Europe, North America)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cases from Clinical Trials, Expanded Access, and Compassionate Use</th>
<th>Locations of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with concomitant aPCC use exceeding the cumulative amount in the Boxed Warning</td>
<td>Europe, North America</td>
</tr>
<tr>
<td>n=1</td>
<td></td>
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<td></td>
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</tbody>
</table>

* 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.

Note: Due to the voluntary nature of postmarketing spontaneous adverse event reports, information may be missing or incomplete. Genentech 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. As of March 31, 2019, due to limitations in reporting of postmarketing spontaneous events, Genentech/Roche will provide information on the number of verified reports but not additional details or assessments of relatedness.

We have robust global systems in place to continuously monitor the safety of a medicine starting from the time it is evaluated in clinical studies. In the postmarketing setting, we have a global drug safety team that collects, processes, evaluates and reports safety information on our medicines. Healthcare authorities and Genentech monitor the totality of safety data to continuously assess the benefit/risk profile of our medicines. We also ask healthcare professionals and patients to voluntarily report any adverse events. We will continue to collect, analyze, and monitor information about any adverse events and report to the FDA per regulation.

References