Patient - Hemlibra and Thrombotic Microangiopathy and Blood Clot (Thrombotic Event) Side Effects

This letter contains information you requested on thrombotic microangiopathy and blood clots (thrombotic events) that happened in people who used Hemlibra® (emicizumab-kxwh). This letter includes studies with the strongest and most relevant data.

This information is provided only for educational purposes and not for use in treatment decisions. You should talk with your healthcare provider for specific information and advice about your condition, your individual situation, healthcare coverage, and any current or potential treatments.

Glossary

Activated prothrombin complex concentrates (aPCC): the bypassing agent, FEIBA®, which contains active and inactive clotting factors.

Prophylaxis: also known as "prophy". A treatment given on a regular schedule to prevent bleeds

rFVIIa: the bypassing agent (NovoSeven® RT), which contains activated factor VII (factor 7a)

Thrombotic events: blood clots that form in blood vessels

Thrombotic microangiopathy (TMA): a potentially life-threatening condition in which blood clots form in small blood vessels that may result in damage to the kidneys and/or other organs

What is Hemlibra?

Hemlibra is FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with or without factor 8 inhibitors.[1]

How many serious side effects of TMA or blood clots (thrombotic events) happened in the Hemlibra HAVEN studies?

Three people taking Hemlibra developed TMA and 2 people developed a blood clot in the HAVEN 1 study.[1,2] HAVEN 1 studied how safe and how well Hemlibra worked to prevent bleeds in people ≥12 years with hemophilia A with inhibitors.

- These cases of TMA and blood clots were reported when on average a cumulative amount of over 100 units/kg per 24 hours of aPCC (FEIBA®) was given for 24 hours or more to treat a bleed while these people were taking Hemlibra.[1,2] Each of these cases improved after treatment with aPCC (FEIBA®) was stopped.[1,2]

One person had a blood clot in HAVEN 3, which studied Hemlibra in people ≥12 years with hemophilia A without inhibitors. This case was not related to use of high dose aPCC (FEIBA®).

The Hemlibra Package Insert is the primary source of information on the known and potential risks associated with Hemlibra for hemophilia A with or without inhibitors. Talk to your treating doctor for questions about Hemlibra.

What happened with each person who developed TMA in HAVEN 1?

- 3 people in the HAVEN 1 study developed TMA after high doses of aPCC (FEIBA®) were used to treat a bleed. (see Table 1 for details)
- 2 cases resolved after aPCC (FEIBA®) treatment was stopped.[1,2] In the third case, TMA improved after aPCC was stopped. This person passed away. The investigator assessed the cause of death as rectal bleeding, unrelated to Hemlibra.
- 1 person restarted Hemlibra treatment with no further TMA events occurring. [1,2]

Table 1. Thrombotic Microangiopathy (TMA) Events in the HAVEN 1 Study[2]

Case	Bleed event (bypassing agents used)	Average aPCC used before TMA developed	rFVIIa usage before TMA developed	TMA resolved?	Restart Hemlibra?
1	2 joints and lower back bleed (aPCC, rFVIIa)	101-150 units/kg per day of aPCC for 3 days	2 doses of rFVIIa 85 µg/kg on 1 day	Resolved	No
2	joint bleed (aPCC)	101-150 units/kg per day of aPCC for 3 days	--	Resolved	Yes
3	rectal bleed (aPCC, rFVIIa)	over 150 units/kg per day of aPCC for 4 days	11 doses of rFVIIa 87 µg/kg over 3 days	Resolving at time of death	No

What happened with each person who developed a blood clot in HAVEN 1 and 3?

- In HAVEN 1, 2 people developed a blood clot after using high doses of aPCC (FEIBA®) to treat a bleed. [1,2] The blood clots resolved after aPCC (FEIBA®) treatment was stopped and no blood thinning medicine was used in either case. One person restarted Hemlibra treatment and has not had another blood clot event.[2] (see Table 2 for details)

Table 2. Blood Clots (Thrombotic Events) in the HAVEN 1 Study[2]

Case	Bleed event (bypassing agents used)	Average aPCC used before blood clot developed	Blood clot resolved?	Restart Hemlibra?
1	joint bleed (aPCC)	over 150 units/kg per day for 3 days	Resolved	Yes
2	joint bleed, shin bleed (aPCC)	101-150 units/kg per day for 2 days	Resolved	No

- In HAVEN 3, 1 person had an acute coronary artery syndrome, a condition resulting from reduced blood flow to the heart.[3] No aPCC (FEIBA®) was used in this case. The event happened around the time of a surgical procedure, and this person had a history of a heart condition. This person continued Hemlibra treatment in the study.

How should bypassing agents be used if taking Hemlibra?

If you take Hemlibra, it's important to talk to your doctor to develop a plan to manage bleeds.[1] Hemlibra cannot be used to treat a breakthrough bleed. Carefully follow your doctor's instructions regarding when to use an on-demand bypassing agent and the exact dose and

schedule of the bypassing agent you should use to treat bleeds.[1] If aPCC (FEIBA®) is needed, talk to your doctor in case you feel you need more than 100 units/kg of aPCC (FEIBA®) total.[1]

Is there additional information about TMA and blood clots (thrombotic events) reported in people taking Hemlibra?

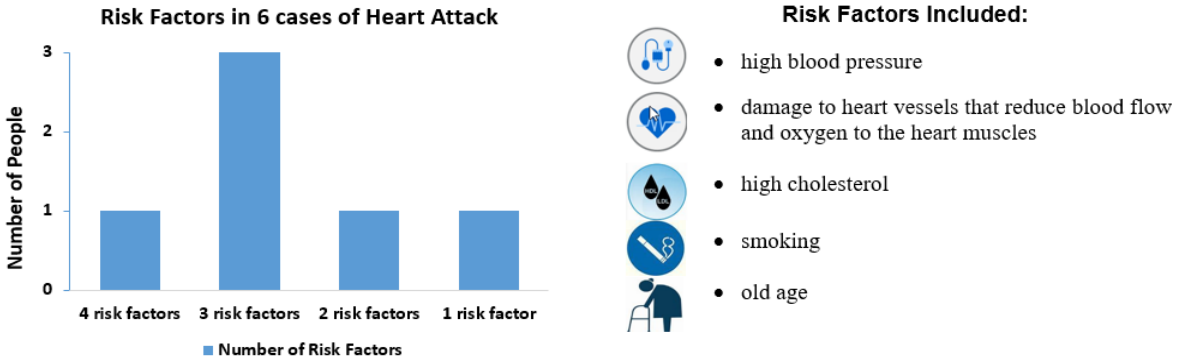
A summary of the clinical factors in people taking Hemlibra who reported TMA and blood clots (thrombotic events) was presented at a scientific meeting.[4] As of December 2019, 4 TMA and 16 blood clots had been reported to Genentech in people taking Hemlibra from clinical trials, expanded access, compassionate use programs, and after FDA approval.

- The summary shows that the TMA and blood clot events reported were associated with aPCC (FEIBA®) or with known existing medical conditions and risk factors.
- All 4 TMA (3 from HAVEN 1 described above, and 1 after FDA approval) and 2 of the blood clots (both from HAVEN 1 described above) were related to use of Hemlibra and aPCC (FEIBA®, at doses >100 U/kg per 24 hours for 24 hours or more).
- Of the remaining 14 blood clots, 2 occurred in people taking Hemlibra for a non-FDA approved use, 3 were related to venous access devices, 1 was not a blood clot based on clinical review, and 8 occurred in 7 people born with hemophilia A (not device related).

Additional details for the 8 non-device related blood clots that occurred in 7 people (1 person had 2 blood clots) born with hemophilia A treated with Hemlibra are provided below. Talk to your treating doctor if you have questions about your treatment or about Hemlibra.

- 8 blood clots happened in 7 people with hemophilia A and included 6 heart attacks, 1 blood clot in the lung, and 1 case with limited information.[4] All of these people had a history of heart disease or risk factors for blood clots.
    - All 6 people who experienced a heart attack had at least 1 risk factor and up to 4 risk factors for heart disease.[4] Four of the 6 people had at least 3 risk factors. (Figure 1)

Figure 1: Risk Factors in People who had Heart Attacks[4]



- The majority of people with blood clots recovered and continued Hemlibra treatment.[4] One person who had ongoing serious and life-threatening medical conditions when the blood clot developed, passed away.

We continue to collect and analyze the information provided for any reported cases. Further data on additional cases will be provided at scientific meetings and in planned publications in 2020.

Where can I find more information about the safety of Hemlibra?

Genentech is committed to transparent, timely communication of safety information about Hemlibra treatment for people with hemophilia A with factor VIII inhibitors. Genentech developed a website for U.S. patients and caregivers, to provide timely and accurate information on targeted serious side effects of interest for Hemlibra, specifically thrombotic microangiopathy (TMA), serious blood clots (thrombotic events), and all fatal events.[5]

Please note, emicizumab-kxwh, the scientific name for Hemlibra is used within this website which was developed by Genentech medical professionals. The current plan is to update the website at least quarterly. The website serves as just one of the ways we will provide safety information about Hemlibra.

- This website for U.S. patients and caregivers may be accessed at the following link: www.emipatientinfo.com.

After FDA approval, safety reports are reported voluntarily from patients and healthcare providers, and the amount of the information received varies. Genentech/Roche does not provide additional details related to serious side effects reported in the postmarketing (after FDA approval) 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 a side effect that could jeopardize the privacy of either the patient or their family, or breach patient confidentiality.

There is no change to the Hemlibra Package Insert. The Hemlibra Package Insert provides FDA-approved information about Hemlibra and is the primary source of information about the known and potential risks of Hemlibra. The Package Insert for Hemlibra includes a Medication Guide which contains FDA-approved information that can help people avoid serious side effects. You should talk to your treating doctor for questions about Hemlibra.

Patient - Thrombotic Microangiopathy and Blood Clots References

1. HemlibraÂ® [package insert]. Genentech, Inc.; South San Francisco, CA. October 2018.

2. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors [supplementary appendix appears online]. N Engl J Med 2017;377:809-818. https://www.ncbi.nlm.nih.gov/pubmed/28691557

3. Data on file (07m8vepmg5bk535j5uh8bkocpk).

4. Lee L, Moreno K, Kuebler P, et al. Summary of thrombotic events or thrombotic microangiopathy events in persons taking emicizumab. Presented at the European Association for Haemophilia and Allied Disorders in Hague, Netherlands; February 5–7, 2020. EAHAD Oral Presentation.

5. Genentech USMA. Emicizumab-kxwh Patient and Caregiver Website: Our Commitment to Provide Transparent and Timely Safety Information About Emicizumab-kxwh. 2018. Available at http://www.emipatientinfo.com/