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

This letter contains information you requested on thrombotic microangiopathy (TMA) 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): A bypassing agent also known as FEIBA® that contains active and inactive clotting factors.

Prophylaxis: Also known as "prophy", it is a treatment given on a regular schedule to prevent bleeds.

rFVIIa: A bypassing agent also known as NovoSeven® RT that contains activated factor VII (factor 7a or FVIIa)

Thrombotic events: Blood clots that form in blood vessels.

Thrombotic microangiopathy (TMA): Thrombotic microangiopathy is 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.

How many serious side effects of TMA or blood clots (thrombotic events) happened in the Hemlibra clinical 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 FVIII 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 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.

An ongoing study called STASEY is studying Hemlibra in people ≥12 years with hemophilia A with inhibitors.[4] A heart attack happened in a 55-year-old man who had risk factors of a smoking history, high blood pressure, and a family history of heart disease. This person did not receive aPCC, and he continued taking Hemlibra. The treating doctor assessed the heart attack as not related to Hemlibra. Another person developed a blood clot at the site of their tooth extraction.

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

Three 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).

- Two cases resolved after aPCC (FEIBA®) treatment was stopped.[1,2]
  - One person restarted Hemlibra treatment with no further TMA events occurring.

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.[1,2]

Table 1: TMA Events in the HAVEN 1 Study[2]

Case	Bleed event (bypassing agents used)	Average aPCC used before TMA	rFVIIa usage before TMA	TMA resolved?	Hemlibra restarted?
1	2 joints and lower back bleed (aPCC, rFVIIa)	101-150 units/kg per day for 3 days	2 doses, each 85 µg/kg, on one day	Yes	No
2	Joint bleed (aPCC)	101-150 units/kg per day for 3 days	--	Yes	Yes
3	Rectal bleed (aPCC, rFVIIa)	over 150 units/kg per day for 4 days	11 doses, each 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?

In HAVEN 1, two 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 (see Table 2 for details).[2]

Table 2: Blood Clots (Thrombotic Events) in HAVEN 1[2]

Case	Bleed events (bypassing agents used)	Average aPCC used before blood clot	Blood clot resolved?	Hemlibra Restarted?
1	Joint bleed (aPCC)	Over 150 units/kg per day for 3 days	Yes	Yes
2	Joint bleed, shin bleed (aPCC)	101-150 units/kg per day for 2 days	Yes	No

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]

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

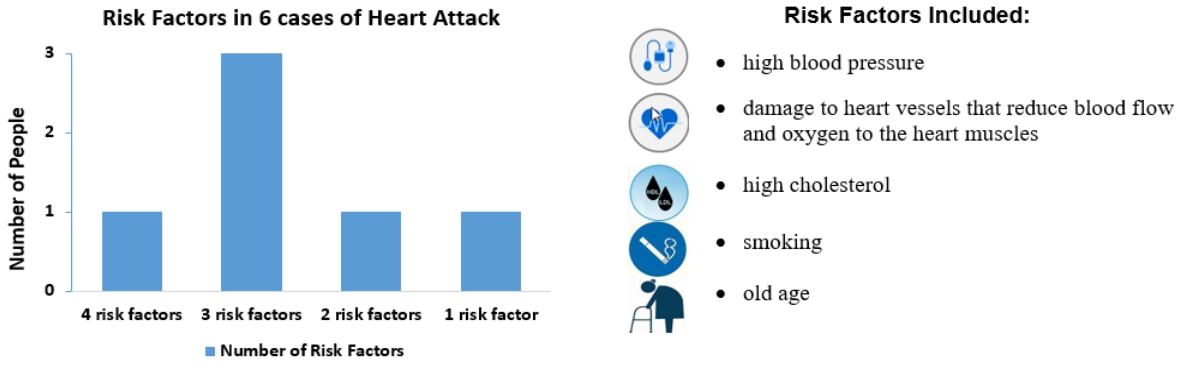
An analysis of clinical factors in reported cases of TMA and blood clots (thrombotic events) in people taking Hemlibra was presented at a scientific meeting.[5] This analysis included a total of 4 TMA and 16 blood clots reported to Genentech as of December 2019 in people using Hemlibra from clinical 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. Eight 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.[5] 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.[5] Four of the 6 people had at least 3 risk factors. (Figure 1)

Figure 1: Risk Factors in People who had Heart Attacks[5]



The majority of people with blood clots recovered and continued Hemlibra treatment.[5] 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. Talk to your treating doctor if you have questions about your treatment or 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. Jimenez-Yuste V, Klamroth R, Castaman G, et al. Second Interim Analysis Results from the STASEY Trial: A Single-arm, Multicenter, Open-label, Phase III Clinical Trial to Evaluate the Safety and Tolerability of Emicizumab Prophylaxis in People with Hemophilia A (PwHA) with FVIII Inhibitors. Presented at the International Society on Thrombosis and Haemostasis Virtual Congress; July 12–14, 2020. ISTH Poster #PB0958.
5. 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.