

## Patient - Hemlibra and Surgeries and Procedures

This letter contains information you requested on surgeries and procedures performed in people with hemophilia A during treatment with Hemlibra<sup>®</sup> (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

**Inhibitors:** In hemophilia A, inhibitors are antibodies against infused factor VIII (factor 8 or FVIII) clotting proteins. These antibodies make the infused factor VIII products not effective.

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

**Thrombotic events:** Blood clots that form in blood vessels.

### What is Hemlibra?

Hemlibra is a medicine that is approved by the Food and Drug Administration (FDA) for prophylaxis in adults and children with hemophilia A, with or without FVIII inhibitors.<sup>1</sup>

### What were the HAVEN trials that studied Hemlibra?

Four Phase 3 trials studied how safe and how well Hemlibra worked to prevent bleeds in people with hemophilia A with or without FVIII inhibitors.<sup>1</sup>

- The HAVEN 1, 3, and 4 trials enrolled adult and adolescents, 12 years or older, with hemophilia A with or without FVIII inhibitors.<sup>1</sup>
- The HAVEN 2 trial enrolled children less than 12 years (or 12-17 years if they weighed <40 kg or 88 lbs) with hemophilia A with FVIII inhibitors.<sup>1</sup>

### Were surgeries or procedures performed in people treated with Hemlibra in the HAVEN clinical trials?<sup>2</sup>

The HAVEN trials were not intended to study the outcomes of surgeries in people taking Hemlibra. People could not enroll in the trials if they had a planned surgery. Certain elective minor procedures were permitted and unplanned surgeries occurred during the HAVEN studies. These surgeries were managed by the treating doctor.

### *How many surgeries occurred in the HAVEN trials in people taking Hemlibra?*<sup>2</sup>

A total of 233 surgeries were performed in 126 people treated with Hemlibra.






- 215 minor surgeries and procedures were performed in 115 people

- 18 major surgeries were performed in 18 people



***What minor surgeries were performed in people taking Hemlibra in the HAVEN trials and how were they managed?<sup>2</sup>***

Most minor surgeries (66%, or 141 out of 215) were managed without preventive clotting factor.

- Most of these (91%, or 128 out of 141) had no treated bleeds after the surgery.

<p>64 dental procedures</p> 	<ul style="list-style-type: none"> <li>• No preventive clotting factor was used in 42 dental procedures <ul style="list-style-type: none"> <li>• 29 out of 42 had no bleeds after surgery</li> <li>• 13 out of 42 had bleeds that occurred after surgery. Nine bleeds were treated with clotting factor and 4 bleeds were not treated</li> </ul> </li> <li>• Out of 22 dental procedures performed with use of preventive clotting factor, 5 bleeds occurred after surgery and were treated with clotting factor</li> </ul>
<p>34 venous access device or port procedures</p> 	<ul style="list-style-type: none"> <li>• No preventive clotting factor was used in 25 procedures <ul style="list-style-type: none"> <li>• 23 out of 25 had no bleeds after surgery</li> <li>• 2 out of 25 had bleeds that occurred after surgery. 1 was treated with clotting factor and 1 was not treated</li> </ul> </li> <li>• Out of 9 procedures performed with use of preventive clotting factor, 2 bleeds occurred after surgery and were treated with clotting factor</li> </ul>
<p>30 endoscopic procedures</p> 	<ul style="list-style-type: none"> <li>• An endoscopic procedure is one in which an instrument is introduced into the body to give a view of its internal parts</li> <li>• No preventive clotting factor was used in 17 procedures <ul style="list-style-type: none"> <li>• No bleeds occurred after surgery in any of the 17 cases</li> </ul> </li> </ul>
<p>25 joint procedures</p> 	<ul style="list-style-type: none"> <li>• No preventive clotting factor was used in 12 joint procedures <ul style="list-style-type: none"> <li>• 11 out of 12 had no bleeds after surgery</li> <li>• 1 out of 12 had bleeding that occurred after surgery and was treated with clotting factor</li> </ul> </li> </ul>
<p>62 other surgeries and procedures</p> 	<ul style="list-style-type: none"> <li>• No preventive clotting factor was used in 45 procedures <ul style="list-style-type: none"> <li>• 41 out of 45 had no bleeds after surgery</li> <li>• 4 out of 45 had bleeds that occurred after surgery. 2 bleeds were treated with clotting factor and 2 bleeds were not treated</li> </ul> </li> </ul>

## **What major surgeries were performed in people taking Hemlibra in the HAVEN trials and how were they managed?<sup>2</sup>**

	<p>The most common type of major surgeries were joint surgeries, including joint arthroplasties and synovectomies.</p> <ul style="list-style-type: none"><li>• Joint arthroplasties are joint replacements or joint reconstruction surgeries.<ul style="list-style-type: none"><li>➤ 5 major joint arthroplasties were performed on ankles, hips, and knees</li></ul></li><li>• Synovectomies are surgeries performed to remove inflamed synovial tissue, which is a layer that lines the joints or tendons<ul style="list-style-type: none"><li>➤ 4 major synovectomies were performed</li></ul></li></ul>
	<p>Some other types of major surgeries included (not a complete list):</p> <ul style="list-style-type: none"><li>• Open reduction of fracture (procedure performed to help correct a fracture)</li><li>• Muscle suture (procedure to stitch together a muscle wound)</li></ul>

Preventive clotting factor was used for 15 out of the 18 major surgeries (83%). Of these 15 cases, 12 had no bleeds after the surgery. In the 3 cases with bleeding after surgery:

- One bleed occurred after surgery and was treated with clotting factor.
- Two bleeds that occurred after surgery were not treated.

In the 3 major surgeries that used no preventive clotting factor, no bleeds occurred after surgeries.

## **What are safety results from the surgeries performed in the HAVEN trials?<sup>2</sup>**

No deaths occurred as a result of any surgery performed in people with hemophilia A with or without FVIII inhibitors. No blood clots (thrombotic events) occurred as a result of any surgery.

## **Have other surgeries been reported in people taking Hemlibra?**

STASEY is an ongoing Phase 3b study that is evaluating Hemlibra prophylaxis in adult and adolescents, 12 years or older, with hemophilia A with FVIII inhibitors.<sup>3,4</sup> As of the most recent analysis of this study (data as of May 2019), there were 31 minor surgeries in 22 people and 9 major unplanned surgeries in 8 people.

- Most of the minor surgeries (20 out of 31, 64.5%) were managed without additional preventative coagulation factor.
  - Minor surgeries included dental, skin-related, venous access device/port-related, joint, blood vessel-related procedures, nose bleed treatment, and laser eye surgery.
- Of the 9 major surgeries, 8 (89%) were managed with preventative coagulation factor (most often with rFVIIa). Four of the surgeries had bleeds that required treatment, 2 had bleeds that didn't require treatment, and 3 had no bleeds after the surgery.
  - Major surgeries included joint arthroplasties (replacements or reconstructions), joint fusions, amputation, treatment for leg fracture, surgical removal of hemorrhoids and polyps, and an imaging test to look at the arteries of the heart.

Outside of the HAVEN trials and STASEY, there have been reports of surgeries in people taking Hemlibra prophylaxis. Some of the surgeries and procedures described include an emergency appendectomy, hernia repair, circumcision, vasectomy, urethroplasty (repair of the urethra), endoscopy (a procedure to put a scope to examine internal parts of the body), dental procedures such as tooth extractions and dental crown placement, ear tube removal, hip replacements, knee replacements, and inserting or removing venous access devices or ports.<sup>5-21</sup>

## **Talk to your treating doctor if a surgery or procedure is needed and you are taking Hemlibra prophylaxis.**

Talk to your treating doctor and develop a plan for any surgeries or procedures that may be performed if you are taking Hemlibra prophylaxis.

## **Hemlibra Surgeries and Procedures References**

1. Hemlibra® [package insert]. Genentech, Inc.; South San Francisco, CA. October 2018.
2. Santagostino E, Oldenburg J, Chang T, et al. Surgical experience from four phase III studies (HAVEN 1-4) of emicizumab in persons with haemophilia A (PwHA) with or without FVIII inhibitors. Presented at the Congress of the International Society on Thrombosis and Haemostasis in Melbourne, Australia; July 6–10, 2019. ISTH Oral Presentation.
3. Castaman G, Hovinga J, Schutgens R, et al. Surgical Experience from the Phase III STASEY Trial of Emicizumab Prophylaxis in Persons with Hemophilia A (PwHA) with FVIII Inhibitors: Data from the Second Interim Analysis. Presented at the International Society on Thrombosis and Haemostasis Virtual Congress; July 12–14, 2020. ISTH Poster #PB0939.
4. Castaman G, Santagostino E, Hovinga J, et al. Surgical Experience from the Phase III STASEY Trial of Emicizumab Prophylaxis in Persons with Hemophilia A (PwHA) with FVIII Inhibitors: Data from the Second Interim Analysis. Presented at the International Society on Thrombosis and Haemostasis Virtual Congress; July 12–14, 2020. ISTH Abstract #PB0939. <https://www.isth2020.org/>
5. Zimowski K, Batsuli G, Reding M, et al. Maintaining perioperative hemostasis in patients with severe hemophilia A and inhibitors receiving emicizumab prophylaxis. Presented at the American Society of Hematology Annual Meeting in San Diego, CA; December 1–4, 2018. ASH Poster #635.
6. Barg AA, Avishai E, Budnik I, et al. Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors—a single-center cohort. *Pediatr Blood Cancer*. E-pub Date: [published online ahead of print] July 2019. DOI # [10.1002/pbc.27886](https://doi.org/10.1002/pbc.27886). <https://www.ncbi.nlm.nih.gov/pubmed/31348595>
7. Kanematsu T, Suzuki N, Sanda N, et al. Clinical course and management of surgical emergency in a severe hemophilia A patient under weekly subcutaneous administration of a bispecific antibody to factors IXa and X (ACE910). Presented at the 57th ASH Annual Meeting and Exposition in Orlando, FL; December 5–8, 2015. ASH Poster #1099.
8. Seaman CD, Ragni MV. Emicizumab use in major orthopedic surgery. *Blood Adv* 2019;3:1722-1724. <https://www.ncbi.nlm.nih.gov/pubmed/31171509>
9. Evans MS, Davis CI, Eyster ME. Orthopedic Surgical Experience with Emicizumab: A Case Report. Presented at the Hemostasis and Thrombosis Research Society/ North American Society on Thrombosis and Hemostasis 2019 Scientific Symposium in New Orleans, LA; May 9–11, 2019. HTRS/NASTH Poster. <https://www.eventscribe.com/2019/HTRS/>

10. Kizilocak H, Yukhtman CL, Marquez-Casas E, et al. Management of perioperative hemostasis in a severe hemophilia A patient with inhibitors on emicizumab using global hemostasis assays. *Ther Adv Hematol* 2019;10:2040620719860025. <https://www.ncbi.nlm.nih.gov/pubmed/31275538>
11. Andreani C, Cau I, Navarro R, et al. PB0319 - Management of Surgery in Hemophilia A Patients with Inhibitors during Emicizumab Prophylaxis. Presented at the International Society on Thrombosis and Haemostasis in Melbourne, Australia; July 6–10, 2019. ISTH Abstract #1417.
12. Ebbert PT, Xavier F, Seaman CD, et al. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. *Haemophilia*. E-pub Date: [published online ahead of print] November 2019. DOI # [10.1111/hae.13877](https://doi.org/10.1111/hae.13877). <https://www.ncbi.nlm.nih.gov/pubmed/31746522>
13. McCary I, Guelcher C, Kuhn J, et al. Peri-Procedural Management and Outcomes of Patients with Hemophilia on Emicizumab Prophylaxis. Presented at the American Society of Hematology in Orlando, FL; December 7–10, 2019. ASH Abstract #2396.
14. McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: Bleeding outcomes and surgical procedures. *Haemophilia*. E-pub Date: [published online ahead of print] April 2020. DOI # [10.1111/hae.14005](https://doi.org/10.1111/hae.14005). <https://www.ncbi.nlm.nih.gov/pubmed/32311809>
15. Carulli C. Major orthopaedic surgery in subjects with inhibitors: long-term follow-up and outcomes on a series of 21 patients at a single institution. Presented at the World Federation of Hemophilia Virtual Summit; June 14–19, 2020. WFH Abstract #MED-FP-022 (18). <https://www.wfh.org/virtual-summit/home>
16. Martinelli M, Passeri V, Gatteri V, et al. Rehabilitation and risk of bleeding after orthopedic major surgery in patients in chronic Emicizumab treatment. Presented at the World Federation of Hemophilia Virtual Summit; June 14–19, 2020. WFH Abstract #MTD-PP-041 (275). <https://www.wfh.org/virtual-summit/home>
17. Lewandowska M, Randall N, Maahs J, et al. Real-World Experience with Emicizumab in Persons with Hemophilia A (HA) with or without Inhibitors. Presented at the International Society on Thrombosis and Haemostasis Virtual Congress; July 12–14, 2020. ISTH Abstract #PB0928. <https://www.isth2020.org/>
18. Escobar M, Dunn A, Quon D, et al. A Phase IV, Multicenter, Open-Label Study of Emicizumab Prophylaxis in Persons with Hemophilia a with or without FVIII Inhibitors Undergoing Minor Surgical Procedures. Presented at the 62nd American Society of Hematology Annual Meeting and Exposition in San Diego, CA; December 5–8, 2020. ASH Abstract #1786. <https://www.hematology.org/meetings/annual-meeting>
19. Escobar M, Dunn A, Quon D. A Phase IV, Multicenter, Open-label Study of Emicizumab Prophylaxis in Persons with Hemophilia A with or Without FVIII Inhibitors Undergoing Minor Surgical Procedures. Presented at the 62nd American Society of Hematology Annual Meeting and Exposition in San Diego, CA; December 5–8, 2020. ASH Poster #1786.
20. Vagreicha A, Stanco J, Ulus D, et al. Real-World Experience Using Emicizumab Prophylaxis for Hemophilia a: Single-Center Experience. Presented at the 62nd American Society of Hematology Annual Meeting and Exposition in San Diego, CA; December 5–8, 2020. ASH Abstract #1791. <https://www.hematology.org/meetings/annual-meeting>
21. Vagreicha A, Stanco J, Ulus D. Real world experience using Emicizumab prophylaxis for Hemophilia. Presented at the 62nd American Society of Hematology Annual Meeting and Exposition in San Diego, CA; December 5–8, 2020. ASH Poster #1791.