

HEMLIBRA® (emicizumab-kxwh) IN HEMOPHILIA A WITH INHIBITORS

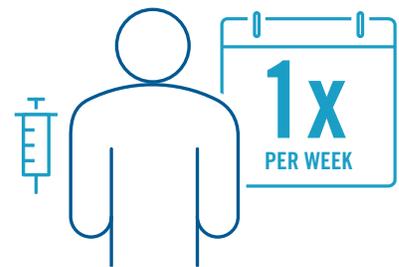
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About HEMLIBRA

HEMLIBRA® (emicizumab-kxwh) is approved by the FDA as a prophylactic medicine used to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.¹ It is given once a week subcutaneously (under the skin).

- **FIRST** new FDA-approved medicine to treat hemophilia A with inhibitors in nearly 20 years
- **FIRST** bispecific monoclonal antibody approved to treat hemophilia A with inhibitors
- Bridges factors IXa and X in the blood clotting cascade
- **ONLY** treatment option for hemophilia A with inhibitors that can be self-administered once weekly by injection subcutaneously
- Provided improvement in Physical Health Score of the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire



About Hemophilia A With Inhibitors

Hemophilia A is a rare, genetic blood disease where missing or faulty blood clotting factor VIII prevents blood from clotting normally. This can cause frequent bleeding, especially into the joints or muscles.¹ These bleeds often cause pain² and can lead to chronic swelling, deformity, reduced mobility and long-term joint damage.³ Factor VIII replacement therapy is a standard treatment for people with hemophilia A, but in some people, their immune systems recognize this as a foreign substance and generate antibodies to attack it. These antibodies are called inhibitors.²

Important Safety Information

What is the most important information to know about HEMLIBRA?

HEMLIBRA increases the potential for blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow the healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule one should use. Cases of thrombotic microangiopathy and thrombotic events were reported 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.

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Please see the following pages and HEMLIBRA full Prescribing Information including Most Serious Side Effects for Important Safety Information.

About Hemophilia A

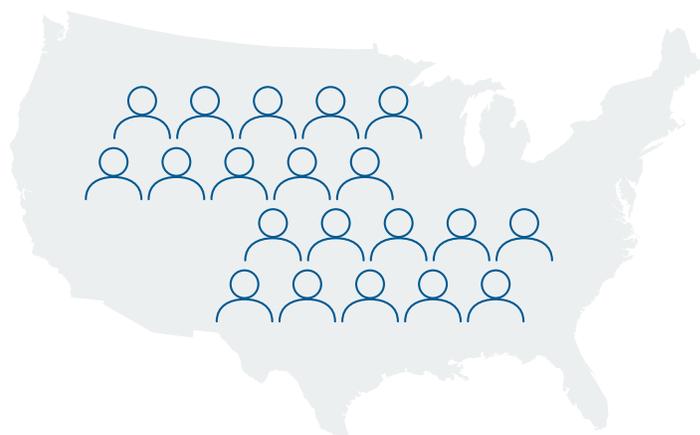
Hemophilia occurs more frequently in males than females.²

NEARLY 20,000

PEOPLE IN THE U.S. HAVE HEMOPHILIA;
HEMOPHILIA A IS THE MOST COMMON TYPE²

ABOUT 50-60%

OF PEOPLE WITH HEMOPHILIA A HAVE A
SEVERE FORM OF THE DISORDER²



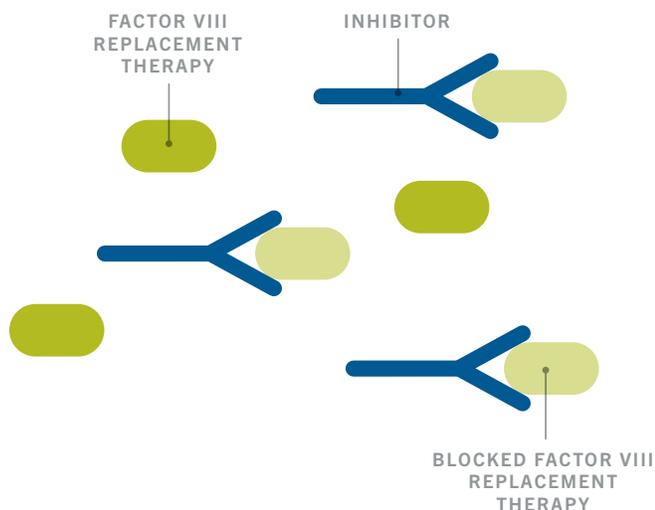
 = 1,000 PEOPLE

About Hemophilia A With Inhibitors

ABOUT 20-30%

OF PEOPLE WITH HEMOPHILIA A CAN DEVELOP
INHIBITORS THAT BIND TO AND BLOCK THE EFFICACY
OF FACTOR VIII REPLACEMENT THERAPY.⁴

Inhibitors make it difficult, if not impossible in some people, to obtain a level of factor VIII sufficient to control bleeding.^{5,6,7} Management of bleeding in people with inhibitors can be a major challenge.



Important Safety Information (continued)

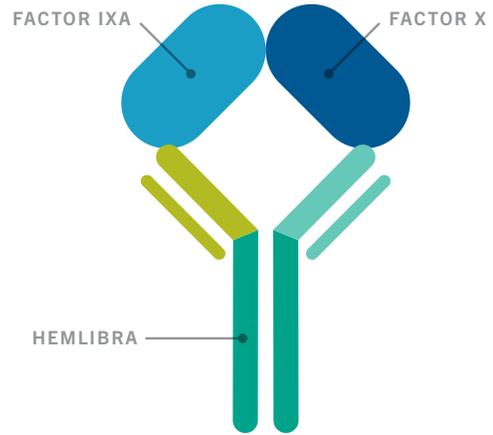
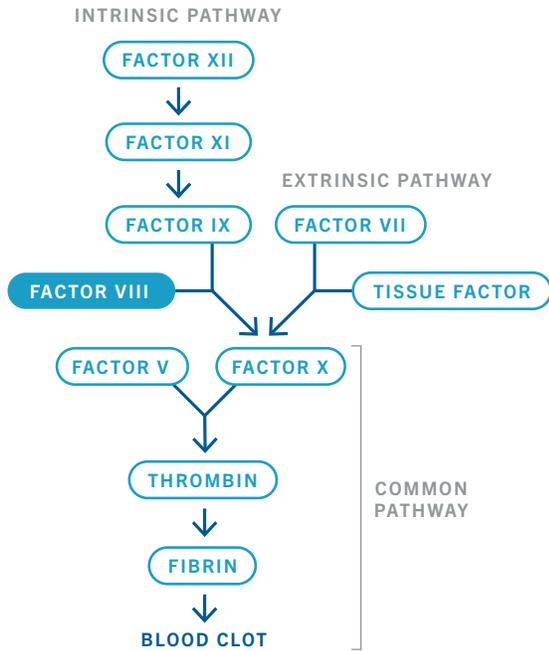
HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to one's kidneys, brain, and other organs. Patients should get medical help right away if they have any of the following signs or symptoms during or after treatment with HEMLIBRA:
 - confusion
 - swelling of arms and legs
 - stomach (abdomen) or back pain
 - feeling sick
 - weakness
 - yellowing of skin and eyes
 - nausea or vomiting
 - decreased urination

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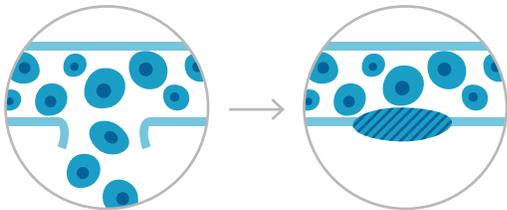
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How HEMLIBRA May Work (Proposed Mechanism of Action)¹



Clotting factors activate each other to form a blood clot, or coagulate. These processes are known as the **coagulation cascade**. People with hemophilia A do not have enough functional natural protein factor VIII.

HEMLIBRA is a bispecific factor IXa- and factor X-directed antibody designed to activate the natural coagulation cascade and restore the blood clotting process for hemophilia A.



By replacing the function of natural activated factor VIII, HEMLIBRA **promotes blood clotting**.



HEMLIBRA is a different type of molecule than activated factor VIII, and is therefore **not expected to induce inhibitors or be affected by inhibitors**.

HEMLIBRA has a long half-life of approximately 4 weeks, which is related to the amount of time the medicine remains active in the body.

Important Safety Information (continued)

- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in one's arm, leg, lung or head. Patients should get medical help right away if they have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:
 - swelling in arms or legs
 - chest pain or tightness
 - feel faint
 - eye pain or swelling
 - pain or redness in the arms or legs
 - fast heart rate
 - headache
 - trouble seeing
 - shortness of breath
 - cough up blood
 - numbness in the face

If aPCC (FEIBA®) is needed, patients should talk to their healthcare provider in case they feel they need more than 100 U/kg of aPCC (FEIBA®) total.

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Please see the following pages and HEMLIBRA full Prescribing Information including Most Serious Side Effects for Important Safety Information.

HEMLIBRA Efficacy¹

The FDA approval of HEMLIBRA is based on positive results from a Phase III clinical study in adolescents and adults (HAVEN 1), and interim results from a pivotal clinical study in children (HAVEN 2).

In the HAVEN 1 study of 109 adolescents and adults (12 years and older) with hemophilia A with inhibitors, once weekly preventative (prophylaxis) administration of HEMLIBRA substantially reduced treated bleeds compared to on-demand (episodic) or preventative use of bypassing agents (BPAS):

Primary Endpoint

87% REDUCTION

IN TREATED BLEEDS WITH HEMLIBRA PROPHYLAXIS COMPARED TO NO PROPHYLAXIS (95% CONFIDENCE INTERVAL [CI]: 72.3; 94.3, P<0.0001)

62.9% vs. 5.6%

OF PEOPLE WHO RECEIVED HEMLIBRA PROPHYLAXIS HAD ZERO BLEEDS (95% CI: 44.9, 78.5)

WHO RECEIVED NO PROPHYLAXIS (95% CI: 0.1, 27.3)

Secondary Endpoints

Improvements in bleed rate with HEMLIBRA prophylaxis compared to no prophylaxis were consistent across all secondary bleed endpoints, including an:

80% REDUCTION

IN ALL BLEEDS (95% CI: 62.5; 89.8, P<0.0001)

89% REDUCTION

IN TREATED JOINT BLEEDS (95% CI: 48; 97.5, P=0.0050)

92% REDUCTION

IN TREATED SPONTANEOUS BLEEDS (95% CI: 84.6; 96.3, P<0.0001)

95% REDUCTION

IN TREATED TARGET JOINT BLEEDS (95% CI: 77.3; 99.1, P=0.0002)

Important Safety Information (continued)

How should patients use HEMLIBRA?

HEMLIBRA may interfere with laboratory tests that measure how well blood is clotting and may cause a false reading. Patients should talk to their healthcare provider about how this may affect their care.

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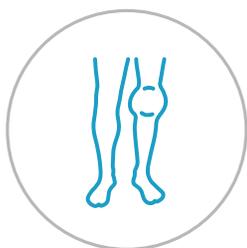
HEMLIBRA Efficacy¹

The HAVEN 1 study is the first to be designed to directly compare the effects of different prophylaxis therapies in the same person with hemophilia A with inhibitors. This first-of-its-kind intra-patient analysis showed a statistically significant:

79% REDUCTION

IN TREATED BLEEDS WITH HEMLIBRA PROPHYLAXIS COMPARED TO PREVIOUS PROPHYLAXIS WITH A BPA
(95% CI: 51.4; 91.1, P=0.0003)

An improvement in Physical Health Score of the Haem-A-QoL questionnaire was observed with HEMLIBRA prophylaxis compared to no prophylaxis. This was measured at 25 weeks and evaluated hemophilia-related symptoms and physical function including:



PAINFUL SWELLINGS



PRESENCE OF JOINT PAIN



PAIN WITH MOVEMENT



DIFFICULTY WALKING FAR

HAVEN 2 is a single-arm, multicenter, open-label, clinical study in children younger than 12 years of age with hemophilia A with inhibitors. In an interim efficacy analysis, annualized bleed rate and percent of subjects with zero bleeds were calculated for 23 children who received once weekly HEMLIBRA prophylaxis. After a median observation time of 38.1 weeks, this interim analysis showed that:

87%

OF CHILDREN WHO RECEIVED HEMLIBRA PROPHYLAXIS FOR AT LEAST 12 WEEKS EXPERIENCED ZERO TREATED BLEEDS
(95% CI: 66.4, 97.2)

Important Safety Information (continued)

What are the other possible side effects of HEMLIBRA?

The most common side effects of HEMLIBRA include: redness, tenderness, warmth, or itching at the site of injection; headache; and joint pain.

These are not all of the possible side effects of HEMLIBRA. Patients should call their doctor for medical advice about side effects.

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95.7%

OF CHILDREN EXPERIENCED ZERO TREATED
SPONTANEOUS BLEEDS (95% CI: 78.1, 99.9)

95.7%

OF CHILDREN EXPERIENCED ZERO TREATED
JOINT BLEEDS (95% CI: 78.1; 99.9)

100%

OF CHILDREN EXPERIENCED ZERO TREATED
TARGET JOINT BLEEDS (95% CI: 85.2; 100)

34.8%

OF CHILDREN EXPERIENCED ZERO BLEEDS OVERALL,
WHICH INCLUDES ALL TREATED AND NON-TREATED
BLEEDS (95% CI: 16.4; 57.3)

An intra-patient analysis in the HAVEN 2 study was also conducted to compare the effects of different therapies in the same child (n=13). In this analysis, HEMLIBRA prophylaxis resulted in a:

99% REDUCTION

IN TREATED BLEEDS COMPARED TO PREVIOUS
TREATMENT WITH A BPA EITHER AS PROPHYLAXIS
(N=12) OR ON-DEMAND (N=1)

84.6%

OF CHILDREN ON HEMLIBRA PROPHYLAXIS HAD ZERO
TREATED BLEEDS

HEMLIBRA Pooled Safety¹

In pooled results of 189 patients in HAVEN 1, HAVEN 2 and dose-finding trial, the most common adverse reactions ($\geq 10\%$) observed in people treated with HEMLIBRA were injection site reactions, headache and joint pain (arthralgia).

Important Safety Information (continued)

Side effects may be reported to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. Side effects may also be reported to Genentech at (888) 835-2555.

Please see the HEMLIBRA full Prescribing Information and the Medication Guide, including **Serious Side Effects**, for more important safety information.

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- 1 HEMLIBRA (emicizumab-kxwh) Prescribing Information. Genentech, Inc. 2017.
 - 2 Centers of Disease Control and Prevention. Hemophilia Facts. <http://www.cdc.gov/ncbddd/hemophilia/facts.html>. 2014. Accessed June 30, 2016.
 - 3 National Hemophilia Foundation. Types of Bleeds. <https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeds>. Accessed July 10, 2017.
 - 4 NIH. How is Hemophilia Treated? <http://www.nhlbi.nih.gov/health/health-topics/topics/hemophilia/treatment>. Accessed July 8, 2016.
 - 5 Centers of Disease Control and Prevention. Inhibitors. <https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html>. 2014. Accessed June 30, 2016.
 - 6 Whelan SF, et al. Distinct Characteristics of Antibody Responses Against Factor VIII in Healthy Individuals and in Different Cohorts of Hemophilia A Patients. *Blood* 2013; 121:1039–48. Accessed July 10, 2017.
 - 7 National Hemophilia Foundation. What is an Inhibitor. <https://www.hemophilia.org/Bleeding-Disorders/Inhibitors-Other-Complications/Inhibitors-for-Consumers/What-is-an-Inhibitor>. Accessed August 31, 2017.
 - 8 American Society of Hematology Blood Journal. F8 gene Mutation Type and Inhibitor Development in Patients with Severe Hemophilia A: systematic review and meta-analysis. <http://www.bloodjournal.org/content/119/12/2922.long?sso-checked=true>. Accessed August 31, 2017.

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