HEMLIBRA® (emicizumab-kxwh) IN HEMOPHILIA A WITH OR WITHOUT FACTOR VIII INHIBITORS

Media Inquiries:
(650) 467-6800

HEMLIBRA™
emicizumab-kxwh
injection for subcutaneous use | 150 mg/mL

About Hemlibra

Hemlibra® (emicizumab-kxwh) is approved by the FDA as a prophylactic (preventative) treatment to prevent or reduce the frequency of bleeding episodes in adults and children, ages newborn and older, with hemophilia A with or without factor VIII inhibitors.[1] It is administered subcutaneously (under the skin) and only once weekly, every two weeks or every four weeks. In pivotal trials, Hemlibra significantly reduced treated bleeds compared to no prophylaxis (HAVEN 1, HAVEN 2, HAVEN 3) and demonstrated clinically meaningful bleed control (HAVEN 4).

- **FIRST AND ONLY** medicine to significantly reduce treated bleeds in prospective intra-patient analyses:
  - Compared to prior treatment with factor VIII prophylaxis in people with hemophilia A without factor VIII inhibitors
  - Compared to prior treatment with bypassing agent (BPA) prophylaxis in people with hemophilia A with factor VIII inhibitors
- **ONLY** approved medicine for hemophilia A that can be self-administered subcutaneously at multiple dosing options
- The efficacy and safety of Hemlibra has been demonstrated in one of the **LARGEST PIVOTAL CLINICAL TRIAL PROGRAMS** in hemophilia A
- **FIRST** new class of medicine to treat hemophilia A in nearly 20 years
- Bispecific monoclonal antibody that bridges factors IXa and X to help restore the blood clotting cascade

Select Important Safety Information

Hemlibra increases the potential for blood to clot. Patients should carefully follow their healthcare provider's instructions regarding when to use an on-demand bypassing agent or factor VIII, and the dose and schedule to use for breakthrough bleed treatment. Hemlibra may cause serious side effects when used with activated prothrombin complex concentrate (aPCC; FEIBA®), including thrombotic microangiopathy (TMA) and blood clots (thrombotic events). 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. Hemlibra may interfere with laboratory tests that measure how well a patient's blood is clotting and may cause a false reading.

Important Safety Information

What is Hemlibra?

Hemlibra is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children, ages newborn and older, with hemophilia A with or without factor VIII inhibitors.

What is the most important information to know about Hemlibra?

Hemlibra increases the potential for blood to clot. Patients should carefully follow their healthcare provider's instructions regarding when to use an on-demand bypassing agent or factor VIII, and the dose and schedule to use for breakthrough bleed treatment.

(continued on next page)

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

About Hemophilia A

Hemophilia A is a rare, genetic bleeding disorder where a protein called factor VIII is missing or faulty, preventing blood from clotting normally. This can cause frequent and spontaneous bleeding, including into the joints or muscles.[2] These bleeds may cause pain[2] and can lead to chronic swelling, deformity, reduced mobility and long-term joint damage.[3]

Some people may also experience repeated bleeding into the same joints, called target joints, that can result in degenerative joint disease.[4]

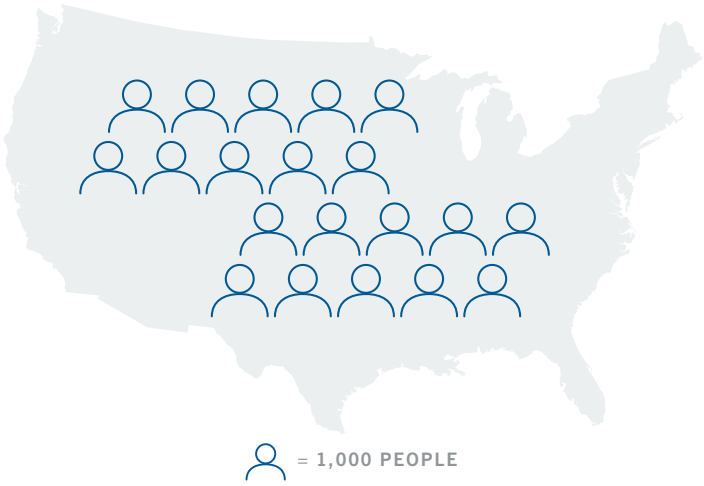
Hemophilia occurs more frequently in males than females.[2]

NEARLY 20,000

PEOPLE IN THE U.S. HAVE HEMOPHILIA; HEMOPHILIA A IS THE MOST COMMON TYPE – ABOUT FOUR TIMES AS COMMON AS HEMOPHILIA B[2]

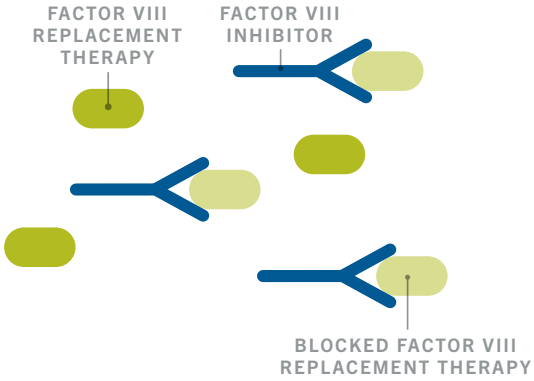
ABOUT 50-60%

OF PEOPLE WITH HEMOPHILIA A HAVE A SEVERE FORM OF THE DISORDER[2]



About Hemophilia A With Factor VIII Inhibitors

In some people with hemophilia A, their immune systems recognize factor VIII replacement therapy, which has been the recommended standard of care treatment, as a foreign substance and generate antibodies to attack it. These antibodies are called factor VIII inhibitors.[2]



ABOUT 20-30%

OF PEOPLE WITH SEVERE HEMOPHILIA A CAN DEVELOP FACTOR VIII INHIBITORS.[5,6]

ABOUT 5-7%

OF ALL PEOPLE WITH HEMOPHILIA A, REGARDLESS OF DISEASE SEVERITY, HAVE FACTOR VIII INHIBITORS.[7]

Factor VIII inhibitors make it difficult, if not impossible in some people, to obtain a level of factor VIII sufficient to control bleeding.[8,9,10] Management of bleeding in people with factor VIII inhibitors can be a major challenge.

Important Safety Information (continued)

Hemlibra may cause the following serious side effects when used with activated prothrombin complex concentrate (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:

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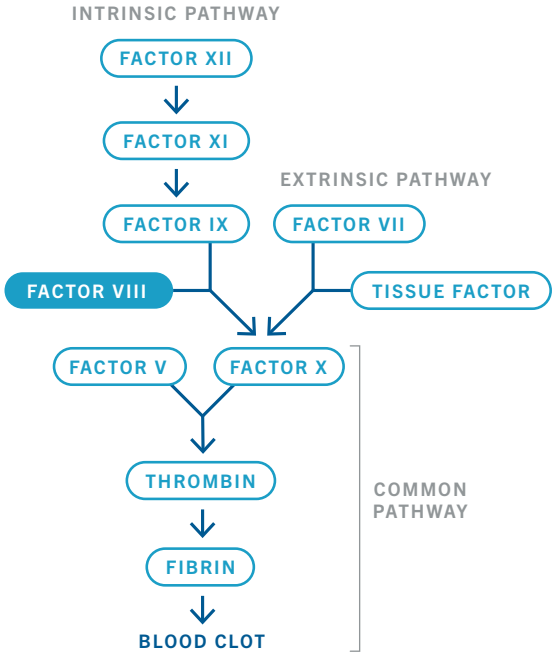
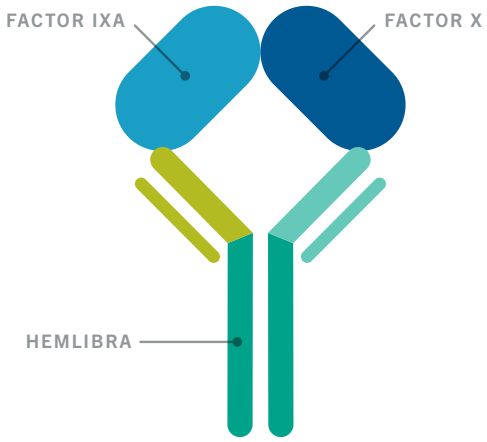
Please see the following pages and Hemlibra full Prescribing Information including Most Serious Side Effects for Important Safety Information.

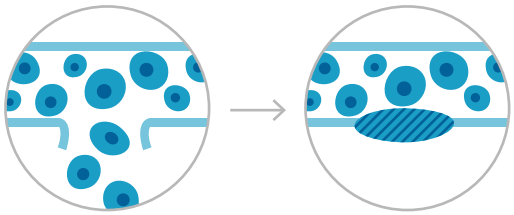
How Hemlibra May Work (Proposed Mechanism of Action)[1]



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 antibody designed to mimic the function of factor VIII and bring together activated factor IX and factor X to continue the natural coagulation cascade and help 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 factor VIII, and it is therefore **not expected to induce factor VIII inhibitors or be affected by factor VIII inhibitors.**

Hemlibra has a long half-life of approximately four weeks, which is the amount of time it takes for the medicine in the body to be reduced in half.

Important Safety Information (continued)

- confusion
- weakness
- swelling of arms and legs
- yellowing of skin and eyes
- stomach (abdomen) or back pain
- nausea or vomiting
- feeling sick
- decreased urination

- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in the 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
  - pain or redness in the arms or legs
  - shortness of breath
  - chest pain or tightness
  - fast heart rate
  - cough up blood
  - feel faint
  - headache
  - numbness in the face
  - eye pain or swelling
  - trouble seeing

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

Hemlibra Efficacy[1]

Hemlibra was studied in one of the largest pivotal clinical trial programs for people with hemophilia A with and without factor VIII inhibitors, which includes the HAVEN 1, HAVEN 2, HAVEN 3, and HAVEN 4 clinical studies (n>350).

The FDA approval of Hemlibra for people with hemophilia A without factor VIII inhibitors is based on positive results from the Phase III HAVEN 3 study in adults and adolescents without factor VIII inhibitors and the Phase III HAVEN 4 study in adults and adolescents with or without factor VIII inhibitors.

The FDA approval of Hemlibra for people with hemophilia A with factor VIII inhibitors is based on positive results from the Phase III HAVEN 1 study in adolescents and adults with factor VIII inhibitors and interim results from the HAVEN 2 study in children with factor VIII inhibitors.

HAVEN 3

EFFICACY[1]

In the HAVEN 3 study of 152 adults and adolescents (12 years or older) with hemophilia A without factor VIII inhibitors, people who received Hemlibra prophylaxis once weekly (n=36) or every two weeks (n=35) experienced significant bleed reductions compared to no prophylaxis (n=18) after 24 weeks:

PRIMARY ENDPOINT

96% REDUCTION

IN TREATED BLEEDS WITH HEMLIBRA PROPHYLAXIS ONCE WEEKLY COMPARED TO NO PROPHYLAXIS (95% CONFIDENCE INTERVAL [CI]: 92.5; 98.0, P<0.0001)

97% REDUCTION

IN TREATED BLEEDS WITH HEMLBBRA PROPHYLAXIS EVERY TWO WEEKS COMPARED TO NO PROPHYLAXIS (95% CI: 93.4; 98.3, P<0.0001)

	Hemlibra prophylaxis once weekly	Hemlibra prophylaxis every two weeks	No prophylaxis
Percent of people who experienced **zero treated bleeds**	**55.6%** (95% CI: 38.1; 72.1)	**60.0%** (95% CI: 42.1; 76.1)	**0%** (95% CI: 0.0; 18.5)
Percent of people who experienced **zero to three treated bleeds**	**91.7%** (95% CI: 77.5; 98.2)	**94.3%** (95% CI: 80.8; 99.3)	**5.6%** (95% CI: 0.1; 27.3)

Important Safety Information (continued)

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.

Before using Hemlibra, patients should tell their healthcare provider about all of their medical conditions, including if they:

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

SECONDARY ENDPOINTS

(p<0.0001 for all reductions)

Intra-Patient Comparison: The HAVEN clinical trial program is the first program in hemophilia A to include a non-interventional study (NIS) that allowed researchers to directly and prospectively compare the effects of different prophylaxis therapies within the same person (an intra-patient comparison). In the intra-patient comparison in one arm of HAVEN 3, people who previously received factor VIII prophylaxis treatment in the NIS switched to Hemlibra prophylaxis once weekly (n=48).

The prospective intra-patient comparison showed a statistically significant:

68% REDUCTION

IN TREATED BLEEDS WITH HEMLIBRA PROPHYLAXIS ONCE WEEKLY COMPARED TO PRIOR FACTOR VIII PROPHYLAXIS (95% CI: 48.6; 80.5).

Improvements in bleed rate with Hemlibra prophylaxis compared to no prophylaxis were consistent across all other secondary bleed-related endpoints, including:

Bleed-related endpoint (compared to no prophylaxis)	Hemlibra prophylaxis once weekly	Hemlibra prophylaxis every two weeks
All bleeds	**95% REDUCTION** (95% CI: 90.1; 97.0)	**94% REDUCTION** (95% CI: 89.7; 97.0)
Treated target joint bleeds	**95% REDUCTION** (95% CI: 85.7; 98.4)	**95% REDUCTION** (95% CI: 85.3; 98.2)
Treated spontaneous bleeds	**94% REDUCTION** (95% CI: 84.9; 97.5)	**98% REDUCTION** (95% CI: 94.4; 99.4)
Treated joint bleeds	**96% REDUCTION** (95% CI: 91.5; 98.1)	**97% REDUCTION** (95% CI: 93.0; 98.5)

Important Safety Information (continued)

- are pregnant or plan to become pregnant. It is not known if Hemlibra may harm an unborn baby. Females who are able to become pregnant should use birth control (contraception) during treatment with Hemlibra.
- are breastfeeding or plan to breastfeed. It is not known if Hemlibra passes into breast milk.

Patients should tell their healthcare provider about all the medicines they take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements. Patients should keep a list of them to show their healthcare provider and pharmacist when they get a new medicine.

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

HAVEN 4

EFFICACY[1]

In the single-arm Phase III HAVEN 4 study, 48 patients (12 years or older) with hemophilia A received Hemlibra prophylaxis every four weeks. Results in the expansion cohort (n=41) in people with hemophilia A with factor VIII inhibitors (n=5) or without factor VIII inhibitors (n=36) showed a median observation time of 25.6 weeks:

56.1%

EXPERIENCED ZERO TREATED BLEEDS (95% CI: 39.7; 71.5)

90.2%

EXPERIENCED THREE OR FEWER TREATED BLEEDS (95% CI: 76.9; 97.3)

HAVEN 1

EFFICACY[1]

In the HAVEN 1 study of 109 adolescents and adults (12 years or older) with hemophilia A with factor VIII inhibitors, once-weekly Hemlibra prophylaxis (n=35) significantly reduced treated bleeds compared to no prophylaxis (n=18) after 24 weeks:

PRIMARY ENDPOINT

87% REDUCTION

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

62.9% OF PEOPLE WHO RECEIVED HEMLIBRA PROPHYLAXIS HAD ZERO BLEEDS (95% CI: 44.9; 78.5)

VS.

5.6% WHO RECEIVED NO PROPHYLAXIS (95% CI: 0.1; 27.3)

SECONDARY ENDPOINTS

Intra-Patient Comparison[1]: In the intra-patient comparison in one arm of HAVEN 1, people who previously received BPA prophylaxis treatment in the NIS switched to Hemlibra prophylaxis once weekly (n=49). The prospective intra-patient comparison showed a statistically significant:

79% REDUCTION

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

Important Safety Information (continued)

How should patients use Hemlibra?

Patients should see the detailed "Instructions for Use" that comes with Hemlibra for information on how to prepare and inject a dose of Hemlibra, and how to properly throw away (dispose of) used needles and syringes.

- **Stop (discontinue) prophylactic use of bypassing agents the day before starting Hemlibra prophylaxis.**
- **Patients may continue prophylactic use of factor VIII for the first week of 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.

Improvements in bleed rate with Hemlibra prophylaxis compared to no prophylaxis were consistent across all other secondary bleed-related endpoints, including:

80% REDUCTION

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

89% REDUCTION

IN TREATED JOINT BLEEDS (95% CI: 48.0; 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)

An improvement in the 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

EFFICACY[1]

The pivotal HAVEN 2 single-arm study included children younger than 12 years of age with hemophilia A with factor VIII inhibitors. In an interim efficacy analysis, annualized bleed rate and percent of people with zero bleeds were calculated for 59 children who received Hemlibra prophylaxis once weekly. After a median observation time of 29.6 weeks, this interim analysis showed that:

86.4%

OF CHILDREN WHO RECEIVED HEMLIBRA PROPHYLAXIS FOR AT LEAST 12 WEEKS EXPERIENCED ZERO TREATED BLEEDS (95% CI: 75.0; 94.0)

98.3%

OF CHILDREN EXPERIENCED ZERO TREATED SPONTANEOUS BLEEDS (95% CI: 90.9; 100)

89.8%

OF CHILDREN EXPERIENCED ZERO TREATED JOINT BLEEDS (95% CI: 79.2; 96.2)

Important Safety Information (continued)

What should patients know about lab monitoring?

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

96.6%

OF CHILDREN EXPERIENCED ZERO TREATED TARGET JOINT BLEEDS (95% CI: 88.3; 99.6)

55.9%

OF CHILDREN EXPERIENCED ZERO BLEEDS OVERALL, WHICH INCLUDES ALL TREATED AND NON-TREATED BLEEDS (95% CI: 42.4; 68.8)

In a prospective intra-patient comparison in the HAVEN 2 study (n=18), Hemlibra prophylaxis resulted in:

98% REDUCTION

IN TREATED BLEEDS COMPARED TO PRIOR TREATMENT WITH A BPA EITHER AS PROPHYLAXIS (N=15) OR ON DEMAND (N=3)

77.8%

OF CHILDREN ON HEMLIBRA PROPHYLAXIS HAD ZERO TREATED BLEEDS

Pooled Safety[1]

The most common adverse reactions occurring in 10% or more of people treated with Hemlibra in pooled studies (n=391) were injection site reactions (n=85), headache (n=57) and joint pain (arthralgia; n=59).

Important Safety Information (continued)

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 speak to their healthcare provider for medical advice about side effects.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Patients should not use Hemlibra for a condition for which it was not prescribed. Patients should not give Hemlibra to other people, even if they have the same symptoms that they have. It may harm them. Patients can ask their pharmacist or healthcare provider for information about Hemlibra that is written for health professionals.

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

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

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9. 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.
10. 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.