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## **FDA approves Roche's Hemlibra (emicizumab-kxwh) for haemophilia A with inhibitors**

- **First new medicine in nearly 20 years to treat people with haemophilia A with inhibitors**
- **Hemlibra substantially reduced bleeds in adults and children**
- **Only medicine that can be self-administered once weekly by injection under the skin (subcutaneously)**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the US Food and Drug Administration (FDA) has approved Hemlibra® (emicizumab-kxwh) for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A with factor VIII inhibitors. Nearly one in three people with severe haemophilia A can develop inhibitors to factor VIII replacement therapies, putting them at greater risk for life-threatening bleeds or repeated bleeds that can cause long-term joint damage. In two of the largest pivotal clinical studies for people with haemophilia A with inhibitors, Hemlibra was shown to substantially reduce bleeds in adults and children.

“People with haemophilia A who develop inhibitors face significant challenges preventing bleeds and typically require infusions of medicine multiple times a week, which can be especially difficult for young children and their families,” said Guy Young, MD, Director of Hemostasis and Thrombosis Program, Children’s Hospital Los Angeles, and Professor of Pediatrics, University of Southern California Keck School of Medicine, Los Angeles, California. “This new medicine has been shown to reduce the frequency of bleeds compared to the currently available medicines and only needs to be injected once a week. This could make a meaningful difference for these children.”

“Before Hemlibra, my 7-year-old son needed intravenous infusions that could take up to two hours at least three times a week, so our lives revolved around his treatment,” said Amber Hill, mother of a young boy with haemophilia A with inhibitors. “With Hemlibra, he now has an injection once a week that he has proudly learned to administer himself to help prevent bleeds. Not only has he had fewer bleeds compared to his prior treatment, he has more time to be a kid and we have more quality time as a family because of the new treatment schedule.”

In the phase III HAVEN 1 study, people 12 years of age or older with haemophilia A with inhibitors who received Hemlibra prophylaxis had a statistically significant reduction in treated bleeds of 87% (95% CI: 72.3; 94.3,  $p < 0.0001$ ) compared to those who received no prophylaxis. In a first-of-its-kind intra-patient analysis, Hemlibra prophylaxis resulted in a statistically significant reduction in treated bleeds of 79% (95% CI: 51.4; 91.1,  $p = 0.0003$ ) compared to previous treatment with bypassing agent (BPA) prophylaxis collected in a non-interventional study (NIS) prior to enrolment.

Interim results from the pivotal HAVEN 2 study in children younger than 12 years of age with haemophilia A with inhibitors showed that 87% (95% CI: 66.4; 97.2) of children who received Hemlibra prophylaxis experienced zero treated bleeds. In an intra-patient analysis of 13 children who had participated in the NIS, 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 ( $n = 1$ ). The most common adverse events (AEs) occurring in 10% or more of people treated with Hemlibra were injection site reactions, headache and joint pain (arthralgia).

“Today’s approval of Hemlibra represents an important advancement for people with haemophilia A with inhibitors, who have struggled to manage their bleeding disorder and haven’t had a new medicine in nearly 20 years,” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “We believe Hemlibra will improve protection against bleeds and reduce the treatment administration burden for people with haemophilia A with inhibitors, and we are committed to helping them access this medicine.”

Hemlibra was reviewed by the FDA under Priority Review and granted Breakthrough Therapy Designation by the FDA in people 12 years of age or older with haemophilia A with inhibitors in September 2015. Data from HAVEN 1 and HAVEN 2 are being reviewed under accelerated assessment by the European Medicines Agency (EMA) and submissions to health authorities around the world are ongoing.

Hemlibra is being studied in a robust clinical development programme that includes two additional phase III studies. HAVEN 3 is evaluating Hemlibra prophylaxis dosed once weekly or once every other week in people 12 years of age or older with haemophilia A without inhibitors to factor VIII. HAVEN 4 is evaluating Hemlibra prophylaxis dosed every four weeks in people 12 years of age or older with haemophilia A with or without inhibitors.

#### **About HAVEN 1 (NCT02622321)**

HAVEN 1 is a randomised, multicentre, open-label, phase III study evaluating the efficacy, safety and pharmacokinetics of once-weekly subcutaneous administration of Hemlibra prophylaxis compared to no prophylaxis in adults and adolescents with haemophilia A with inhibitors to factor VIII. The study included 109 patients (12 years of age and older) with haemophilia A with inhibitors to factor VIII, who were previously treated with BPAs on-demand or as prophylaxis. Patients previously treated with on-demand BPAs were randomised in a 2:1 ratio to receive Hemlibra prophylaxis (Arm A) or no prophylaxis (Arm B). Patients previously treated with BPAs as prophylaxis received HEMLIBRA prophylaxis (Arm C). Additional patients previously treated with on-demand BPAs were also enrolled in a separate arm (Arm D). On-demand treatment of breakthrough bleeds with BPAs was allowed per protocol in all arms.

Below is a summary of key data from the HAVEN 1 study.

- The primary endpoint showed a statistically significant reduction in treated bleeds of 87% (95% CI: 72.3; 94.3,  $p < 0.0001$ ) with Hemlibra prophylaxis compared to no prophylaxis.
  - In addition, 62.9% (95% CI: 44.9; 78.5) of patients who received Hemlibra prophylaxis experienced zero treated bleeds compared to 5.6% (95% CI: 0.1; 27.3) of patients who received no prophylaxis.

- All 12 secondary endpoints were positive. In a first-of-its-kind intra-patient analysis, Hemlibra prophylaxis resulted in a statistically significant reduction in treated bleeds of 79% (95% CI: 51.4; 91.1, p=0.0003) compared to previous treatment with BPA prophylaxis collected in the NIS prior to enrolment. Additionally, 70.8% (95% CI: 48.9; 87.4) of patients experienced zero treated bleeds with Hemlibra prophylaxis compared to 12.5% (95% CI: 2.7; 32.4) with previous treatment with BPA prophylaxis during the NIS.
- Improvements in bleed rate with Hemlibra prophylaxis compared to no prophylaxis included an 80% (95% CI: 62.5; 89.8, p<0.0001) reduction in all bleeds, a 92% (95% CI: 84.6; 96.3, p<0.0001) reduction in treated spontaneous bleeds, an 89% (95% CI: 48; 97.5, p=0.0050) reduction in treated joint bleeds and a 95% (95% CI: 77.3; 99.1, p=0.0002) reduction in treated target joint bleeds.
- An improvement in Physical Health Score of the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire was observed with Hemlibra prophylaxis compared to no prophylaxis. This was measured at 25 weeks in adults 18 years of age and older and evaluated haemophilia-related symptoms (painful swellings and presence of joint pain) and physical function (pain with movement and difficulty walking far).

Hemlibra may cause serious side effects when used with aPCC (FEIBA®), including thrombotic microangiopathy (TMA) and blood clots (thrombotic events). 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. As previously reported, three people experienced TMA events and two people experienced serious thrombotic events in the HAVEN 1 study.

#### **About HAVEN 2 (NCT02795767)**

HAVEN 2 is a single-arm, multicentre, open-label, clinical study in children younger than 12 years of age with haemophilia A with inhibitors to factor VIII. The study is evaluating the efficacy, safety and pharmacokinetics of once-weekly subcutaneous administration of HEMLIBRA prophylaxis. The interim efficacy analysis, after at least 12 weeks of treatment, included 23 children.

- After a median observation time of 38.1 weeks, the interim analysis showed that 87% (95% CI: 66.4; 97.2) of children who received Hemlibra prophylaxis experienced zero treated bleeds. Interim data also showed:
  - 34.8% (95% CI: 16.4; 57.3) of children experienced zero bleeds overall, which includes all treated and non-treated bleeds.
  - 95.7% (95% CI: 78.1; 99.9) of children experienced zero treated spontaneous bleeds.
  - 95.7% (95% CI: 78.1; 99.9) of children experienced zero treated joint bleeds.
  - 100% (95% CI: 85.2; 100) of children experienced zero treated target joint bleeds.
- In an intra-patient analysis, 13 children who had participated in the NIS had an annualised bleeding rate (ABR) for treated bleeds of 17.2 (95% CI: 12.4; 23.8) on previous treatment with a BPA either as prophylaxis (n=12) or on-demand (n=1) compared to 0.2 (95% CI: 0.1; 0.8) on Hemlibra prophylaxis, corresponding to a 99% reduction in bleed rate. On Hemlibra prophylaxis, 11 children (84.6%) experienced zero treated bleeds.

The most common AEs occurring in 10% or more of people treated with Hemlibra in pooled studies were injection site reactions, headache and joint pain (arthralgia).

### **About Hemlibra**

Hemlibra is a bispecific factor IXa- and factor X-directed antibody. It is designed to bring together factor IXa and factor X, proteins required to activate the natural coagulation cascade and restore the blood clotting process for haemophilia A patients. Hemlibra is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once weekly. Hemlibra was created by Chugai Pharmaceutical Co., Ltd. and is being co-developed by Chugai, Roche and Genentech.

## **About haemophilia A**

Haemophilia A is an inherited, serious disorder in which a person's blood does not clot properly, leading to uncontrolled and often spontaneous bleeding. Haemophilia A affects around 320,000 people worldwide,<sup>1,2</sup> approximately 50-60% of whom have a severe form of the disorder.<sup>3</sup> People with haemophilia A either lack or do not have enough of a clotting protein called factor VIII. In a healthy person, when a bleed occurs, factor VIII brings together the clotting factors IXa and X, which is a critical step in the formation of a blood clot to help stop bleeding. Depending on the severity of their disorder, people with haemophilia A can bleed frequently, especially into their joints or muscles.<sup>1</sup> These bleeds can present a significant health concern as they often cause pain and can lead to chronic swelling, deformity, reduced mobility, and long-term joint damage.<sup>4</sup> A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies.<sup>5</sup> Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII,<sup>6</sup> making it difficult, if not impossible to obtain a level of factor VIII sufficient to control bleeding. Most people with haemophilia A who develop inhibitors will infuse BPA therapies, either on-demand (episodic) or as prophylaxis.

## **About Roche in haematology**

For more than 20 years, Roche has been developing medicines that redefine treatment in haematology. Today, we are investing more than ever in our effort to bring innovative treatment options to people with diseases of the blood. In addition to approved medicines MabThera®/Rituxan® (rituximab), Gazyva®/Gazyvaro® (obinutuzumab), and Venclexta™/Venclyxto™ (venetoclax) in collaboration with AbbVie, Roche's pipeline of investigational haematology medicines includes Tecentriq® (atezolizumab), an anti-CD79b antibody drug conjugate (polatuzumab vedotin/RG7596) and a small molecule antagonist of MDM2 (idasanutlin/RG7388). Roche's dedication to developing novel molecules in haematology expands beyond malignancy, with the development of Hemlibra (emicizumab), a bispecific monoclonal antibody for the treatment of haemophilia A.

## **About Roche**

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry nine years in a row by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2016 employed more than 94,000 people worldwide. In 2016, Roche invested CHF 9.9 billion in R&D and posted sales of CHF 50.6 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit [www.roche.com](http://www.roche.com).

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### **References**

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