

FDA approves Roche's Hemlibra for haemophilia A without factor VIII inhibitors

- **First medicine to significantly reduce treated bleeds compared to prior factor VIII prophylaxis based on an intra-patient comparison**
- **Only medicine that can be self-administered subcutaneously once weekly, every two weeks or every four weeks for haemophilia A with and without factor VIII inhibitors**
- **The efficacy and safety of Hemlibra has been demonstrated in one of the largest pivotal clinical trial programmes in haemophilia A**

Basel, 4 October 2018 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today 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, ages newborn and older, with haemophilia A without factor VIII inhibitors. Hemlibra is now the only prophylactic treatment for people with haemophilia A with and without factor VIII inhibitors that can be administered subcutaneously (under the skin) and at multiple dosing options (once weekly, every two weeks or every four weeks). This approval is based on positive results from the phase III HAVEN 3 and HAVEN 4 studies. Hemlibra prophylaxis led to statistically significant and clinically meaningful reductions in treated bleeds compared to no prophylaxis (primary endpoint) and across all other bleed-related endpoints in the HAVEN 3 study, and showed a clinically meaningful control of bleeding in the HAVEN 4 study.

“Many preventative treatment options for people with haemophilia A without factor VIII inhibitors require intravenous infusions several times a week. Even then, people can still experience bleeds, and there has been a need for more treatment options,” said Michael Callaghan, MD, haematologist, Children’s Hospital of Michigan, Detroit. “The approval of Hemlibra is an important advancement for the entire haemophilia A community, as we now have a new class of medicine for the first time in nearly 20 years. Hemlibra can reduce bleeds, and it offers a new subcutaneous administration once weekly, every two weeks or every four weeks.”

“Today’s approval of Hemlibra reflects our commitment to groundbreaking science and the development of medicines with the potential to redefine the standard of care,” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “Hemlibra is now the only FDA-approved medicine for people with haemophilia A with and without factor VIII inhibitors, based on the efficacy and safety profile demonstrated across four pivotal studies. We want to thank the haemophilia community for their partnership in helping us bring this new option to everyone living with haemophilia A.”

In the phase III HAVEN 3 study, adults and adolescents aged 12 years or older with haemophilia A without factor VIII inhibitors who received Hemlibra prophylaxis once weekly (n=36) or every two weeks (n=35) experienced a 96% (95% CI: 92.5; 98.0, p<0.0001) and 97% (95% CI: 93.4; 98.3, p<0.0001) reduction in treated bleeds, respectively, compared to those who received no prophylaxis (n=18). Hemlibra is the first medicine to significantly reduce treated bleeds compared to prior factor VIII prophylaxis, which has been the recommended standard of care, as demonstrated by a statistically significant reduction of 68% (95% CI: 48.6;

80.5, $p < 0.0001$) in treated bleeds in a prospective intra-patient comparison ($n=48$) of people who previously received factor VIII prophylaxis in a non-interventional study and switched to Hemlibra prophylaxis. In the single-arm phase III HAVEN 4 study of adults and adolescents aged 12 years or older with haemophilia A with factor VIII inhibitors ($n=5$) and without factor VIII inhibitors ($n=36$), Hemlibra prophylaxis every four weeks ($n=41$) led to clinically meaningful control of bleeding. 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; $n=59$).

Hemlibra was granted Breakthrough Therapy Designation by the FDA for haemophilia A without factor VIII inhibitors. It was also granted Priority Review, a designation given to medicines that the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a serious disease. The company's Marketing Authorisation Application (MAA) variation for haemophilia A without factor VIII inhibitors, which includes data from the HAVEN 3 and HAVEN 4 studies, is under review by the European Medicines Agency (EMA). Submissions to other regulatory authorities around the world are ongoing.

Hemlibra was approved by the FDA in November 2017 for adults and children with haemophilia A with factor VIII inhibitors. It has been studied in one of the largest pivotal clinical trial programmes in people with haemophilia A with and without factor VIII inhibitors, including four pivotal HAVEN studies (HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4).

About HAVEN 3 (NCT02847637)

HAVEN 3 is a randomised, multicentre, open-label, phase III study evaluating the efficacy, safety and pharmacokinetics of Hemlibra prophylaxis versus no prophylaxis (episodic/on-demand factor VIII treatment) in people with haemophilia A without factor VIII inhibitors. The study included 152 patients with haemophilia A (12 years of age or older) who were previously treated with factor VIII therapy either on-demand or for prophylaxis. Patients previously treated with on-demand factor VIII were randomised in a 2:2:1 fashion to receive subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 1.5 mg/kg/wk for at least 24 weeks (Arm A; $n=36$), subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 3 mg/kg/2wks (Arm B; $n=35$) for at least 24 weeks or no prophylaxis (Arm C; $n=18$) for at least 24 weeks. Patients previously treated with factor VIII prophylaxis received subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 1.5 mg/kg/wk until the end of study (Arm D; $n=48$). Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

HAVEN 3 met its primary endpoint and key secondary endpoints. Data from the study showed:

- Hemlibra prophylaxis once weekly or every two weeks resulted in a 96% (95% CI: 92.5; 98.0, $p < 0.0001$) and 97% (95% CI: 93.4; 98.3, $p < 0.0001$) reduction in treated bleeds, respectively, compared to no prophylaxis.
- 55.6% (95% CI: 38.1; 72.1) of people treated with Hemlibra once weekly and 60% (95% CI: 42.1; 76.1) of people treated with Hemlibra every two weeks experienced zero treated bleeds, compared to 0% (95% CI: 0.0; 18.5) of people treated with no prophylaxis.

- 91.7% (95% CI: 77.5; 98.2) of people treated with Hemlibra prophylaxis once weekly and 94.3% (95% CI: 80.8; 99.3) of people treated with Hemlibra prophylaxis every two weeks experienced three or fewer treated bleeds, compared to 5.6% (95% CI: 0.1; 27.3) of people treated with no prophylaxis.
- Hemlibra prophylaxis once weekly or every two weeks resulted in a 95% (95% CI: 85.7; 98.4, $p < 0.0001$) and 95% (95% CI: 85.3; 98.2, $p < 0.0001$) reduction in treated target joint bleeds, respectively, compared to no prophylaxis.
- Hemlibra prophylaxis once weekly or every two weeks resulted in a 95% (95% CI: 90.1; 97.0, $p < 0.0001$) and 94% (95% CI: 89.7; 97.0, $p < 0.0001$) reduction in all bleeds, respectively, compared to no prophylaxis.
- Hemlibra prophylaxis once weekly demonstrated a statistically significant reduction of 68% (95% CI: 48.6; 80.5, $p < 0.0001$) in treated bleeds compared to prior factor VIII prophylaxis based on a prospective intra-patient comparison of people who were previously enrolled in a non-interventional study.
- 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).

About HAVEN 4 (NCT03020160)

HAVEN 4 is a single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety and pharmacokinetics (PK) of subcutaneous administration of Hemlibra dosed every four weeks. The study included 48 patients (12 years of age or older) with haemophilia A with or without factor VIII inhibitors who were previously treated with either factor VIII or bypassing agents, on-demand or as prophylaxis. The study was conducted in two parts: a PK run-in; and an expansion cohort. All patients in the PK run-in (n=7) were previously treated on-demand and received subcutaneous Hemlibra at 6 mg/kg to fully characterise the PK profile after a single dose during four weeks, followed by 6 mg/kg every four weeks for at least 24 weeks. In the expansion cohort (n=41), patients with haemophilia A with factor VIII inhibitors (n=5) and without factor VIII inhibitors (n=36) received subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 6 mg/kg every four weeks for at least 24 weeks. Episodic treatment of breakthrough bleeds with factor VIII therapy or bypassing agents, depending on a patient's factor VIII inhibitor status, was allowed per study protocol.

In the HAVEN 4 study, 56.1% (95% CI: 39.7; 71.5) of people with or without factor VIII inhibitors treated with Hemlibra prophylaxis every four weeks experienced zero treated bleeds and 90.2% (95% CI: 76.9; 97.3) experienced three or fewer treated bleeds.

About Hemlibra (emicizumab)

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 people with haemophilia A. 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, every

two weeks or every four weeks. Hemlibra was created by Chugai Pharmaceutical Co., Ltd. and is being co-developed globally by Chugai, Roche and Genentech. It is marketed in the United States by Genentech as Hemlibra (emicizumab-kxwh), with kxwh as the suffix designated in accordance with Nonproprietary Naming of Biological Products Guidance for Industry issued by the US Food and Drug Administration.

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, ^[1,2] approximately 50-60% of whom have a severe form of the disorder. ^[3] 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. ^[1] 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. ^[4] A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies. ^[5] Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII, ^[6] making it difficult, if not impossible to obtain a level of factor VIII sufficient to control bleeding.

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. Moreover, for the tenth consecutive year, Roche has been recognised as the most sustainable company in the Pharmaceuticals Industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2017 employed about 94,000 people worldwide. In 2017, Roche invested CHF 10.4 billion in R&D and posted sales of CHF 53.3 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.

All trademarks used or mentioned in this release are protected by law.

References

- [1] WFH. Guidelines for the management of haemophilia. 2012 [Internet; cited 2018 July]. Available from: <http://www1.wfh.org/publications/files/pdf-1472.pdf>
- [2] Berntorp E, Shapiro AD. Modern haemophilia care. *The Lancet* 2012; 370:1447-1456.
- [3] Marder VJ, et al. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 6th Edition, 2013. Milwaukee, Wisconsin. Lippincott Williams and Wilkin.
- [4] Franchini M, Mannucci PM. Haemophilia A in the third millennium. *Blood Rev* 2013; 179-84
- [5] Gomez K, et al. Key issues in inhibitor management in patients with haemophilia. *Blood Transfus.* 2014; 12:s319-s329.
- [6] Whelan, SF, et al. Distinct characteristics of antibody responses against factor VIII in healthy individuals and in different cohorts of haemophilia A patients. *Blood* 2013; 121:1039-48.

Roche Investor Relations

Dr. Karl Mahler

Phone: +41 61 68-78503

e-mail: karl.mahler@roche.com

Jon Kaspar Bayard

Phone: +41 61 68-83894

e-mail: jon_kaspar.bayard@roche.com

Dr. Sabine Borngräber

Phone: +41 61 68-88027

e-mail: sabine.borngraeber@roche.com

Dr. Bruno Eschli

Phone: +41 61 68-75284

e-mail: bruno.eschli@roche.com

Dr. Birgit Masjost

Phone: +41 61 68-84814

e-mail: birgit.masjost@roche.com

Dr. Gerard Tobin

Phone: +41 61 68-72942

e-mail: gerard.tobin@roche.com

Investor Relations North America

Loren Kalm

Phone: +1 650 225 3217

e-mail: kalm.loren@gene.com

Dr. Lisa Tuomi

Phone: +1 650 467 8738

e-mail: tuomi.lisa@gene.com