PROPOSAL FOR THE ADDITION OF EMICIZUMAB TO THE WHO CORE LIST OF ESSENTIAL MEDICINES (EML) AND ESSENTIAL MEDICINES LIST FOR CHILDREN (EMLc) FOR THE TREATMENT OF

1) PEOPLE WITH ALL SEVERITIES OF HEMOPHILIA A AND INHIBITORS TO FACTOR VIII

2) PEOPLE WITH SEVERE HEMOPHILIA A WITHOUT INHIBITORS TO FACTOR VIII

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None of the contributors have conflicts of interests to declare.

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Section 1: Summary statement of the proposal

This submission recommends the inclusion of emicizumab as an individual medicine in the core list of the Essential Medicines List (EML) and the Essential Medicines List for Children (EMLc) for the treatment of A) people with all severities of hemophilia A and inhibitors to factor VIII (FVIII) and B) people with severe hemophilia A without inhibitors to FVIII.

The prevalence at birth per 100,000 males is estimated to be 24.6 cases for all severities of hemophilia A, 9.5 cases for severe hemophilia A, 5.0 cases for all severities of hemophilia B, and 1.5 cases for severe hemophilia B *(1)*. According to the prevalence at birth estimates and based on the world population in 2024 *(2)*, the expected number of people born with hemophilia is 1,213,600, of whom 451,000 should have severe hemophilia. The distribution of people with hemophilia (PwH) is similar worldwide; however, survival to adulthood, especially among severely affected individuals, is lower in low- and middle-income countries (LMICs) with restricted access to efficacious coagulation therapies.

Hemophilia A is caused by a deficit in the coagulation cascade protein Factor VIII (FVIII). The severity of hemophilia is defined by a persons' baseline levels of FVIII: FVIII levels of <1% are considered severe, 1-5% are considered moderate, and 5-40% are considered mild *(3)*. Hemophilia is characterized by frequent internal bleeding into joints (most commonly ankles, knees, and elbows) and muscles (most commonly psoas, calf, and thigh). Repeated bleeding into joints and muscles causes hemophilia arthropathy and severe disability. When bleeding occurs in a vital area (e.g., brain, neck, throat, or stomach), it can be fatal.

Treatment for hemophilia A can be either regular *prophylaxis* to prevent bleeding, which is recommended as the standard of care for severe disease *(3)*, or periodic, *on-demand* treatment when bleeding occurs, which is more commonly used for non-severe disease and for people with severe hemophilia in low-income countries (LICs).

In approximately 30% of cases of severe hemophilia A, the body's immune system develops inhibitors to FVIII and infusions of FVIII are no longer possible. In these cases, the traditionally recommended treatments are a) massive doses of FVIII over months and even years to tolerize the patient, called immune tolerance induction (ITI), or b) prophylactic or on-demand infusion of bypassing agents such as recombinant FVIIa or activated prothrombin complex concentrate (PCC). PwH A (PwHA) with persistent inhibitors experience worse outcomes and increased morbidity and death, compared to those without inhibitors, even with the availability of bypassing agents.

Emicizumab is a prophylactic treatment to prevent bleeding in all PwHA, regardless of their inhibitor status. It is not used to stop active bleeding. When active bleeding occurs, FVIII or a bypassing agent is infused. Emicizumab does not require intravenous administration; it is injected subcutaneously once every 1, 2 or 4 weeks.

The evidence indicates that emicizumab is dramatically more efficacious in preventing internal bleeding than current bypassing agents for PwHA and FVIII inhibitors *(4)*. Moreover, it has been shown to be more cost-effective than either ITI or bypassing agents in multiple countries.

The evidence also indicates that emicizumab lowers the annual bleeding rate (ABR) in individuals with severe hemophilia A without inhibitors, compared to on-demand treatment or prophylaxis with FVIII concentrates.

This submission is made in support of the inclusion of emicizumab on the WHO Essential Medicines Core List. As the bleeding patterns, treatment comparators, and evidence vary between those with and without inhibitors, separate cases will be made for:

1) PwHA of all severities and inhibitors to FVIII.

2) people with severe hemophilia A without inhibitors to FVIII.

Section 2: Consultation with WHO technical departments

The WFH originally proposed the inclusion of Emicizumab in the square box listing as a therapeutic alternative to plasma-derived FVIII in the EML and EMLc. This recommendation, along with other recommended therapeutic alternatives to plasma-derived FVIII, was prepared in response to the official request received on behalf of the previous WHO Director of Health Products Policy and Standards, Dr Clive Ondari, in August 2022. The WFH recommendations were reviewed by the WHO Expert Committee, which concluded that the FVIII mimetic, a bispecific monoclonal antibody, emicizumab, was not a therapeutic alternative to FVIII, but rather could be used as a separate treatment strategy for patients with hemophilia A. The Committee stated that a separate application could be considered for the independent inclusion of emicizumab in the Model Lists in the future. Since these recommendations were published, the WFH has held a virtual meeting with the EML secretariat in the fall of 2023, followed by several written letters exchanged with the WHO Health Products Policy and Standards department (see Appendix 1 to Appendix 3) and an in-person meeting at the WHO Headquarters in Geneva on May 30, 2024 with the following WHO representatives:

- Dr. Deusdedit Mubangizi, Director, Health Products Policy and Standards
- Dr. Lorenzo Moja, Secretariat of the Model List of Essential Medicines
- Bernadette Cappello, Secretariat of the Model List of Essential Medicines
- Dr. Yuyun Maryuningsih, Team Lead, Blood and other Products of Human Origin
  Dr. Junping Ju, Blood and other Products of Human Origin team, the Designated Technical Officer for the WFH as a Non-State Actor in Official Relations with the WHO

During this meeting, the WFH presented its key recommendations in relation to the medicines currently listed and those recommended to be included in the EML and EMLc. As an outcome of this discussion and based on the recommendation of the WHO, the WFH has prepared three submissions for consideration by the WHO Expert Committee as part of the 2025 review of the Model Lists of Essential Medicines:) Removal of cryoprecipitate (non-pathogen reduced) from the Model Lists, limitation of pathogen-reduced cryoprecipitate to indications outside the treatment of hemophilia A and von Willebrand Disease (VWD), transfer of the listing of plasma-derived FVIII and FIX concentrates from complementary to core lists of EML and EMLc, and removal of FIX complex as a therapeutic alternative to FIX concentrates 2) inclusion of recombinant FVIII and FIX concentrates in EML and EMLc; and 3) inclusion of emicizumab, a FVIII mimetic bispecific antibody, in EML and EMLc.

Three draft proposals were also submitted to the EML secretariat and Blood and Other Products of Human Origin team to obtain detailed feedback prior to submission of the final proposals. The WHO EML secretariat provided written comments that were considered while finalizing the submissions.

Section 3: Other organizations(s) consulted and/or supporting the submission

The WFH held information sessions with national patient organizations that are the WFH national member organizations who represent bleeding disorder communities from all regions of the world. The WFH also informed and consulted with multiple organizations during the development of the three submissions, including:

- European Haemophilia Consortium supports the three WFH submissions and have provided a support letter (see Appendix 4)
- European Association for Haemophilia and other Allied Disorders supports the three WFH submissions and will be submitting a support letter during the WHO public commenting period.
- International Patient Organisation for Primary Immunodeficiencies supports the three WFH submissions and have provided a support letter (see Appendix 5)
- Rare Diseases International supports the three WFH submissions and have provided a support letter (see appendix 6)
- International Society on Thrombosis and Haemostasis supports this submission have provided a support letter (see appendix 7).

Multiple national patient associations have expressed their support for the three WFH proposals and are preparing a joint letter of support, that will be submitted to the WHO during the public commenting period. The list of WFH national member organizations is available at: https://wfh.org/find-local-support/#NMOs

Section 4: Key information summary table for the proposed medicine(s)

INN	Emicizumab		
ATC Code	B02BX06		
ICD Classification *(5)*	a) 3B10.1 Hereditary factor VIII deficiency with anti-factor VIII inhibitor b) 3B10.0 Haemophilia A		
Indications	Treatment of a) people with all severities of hemophilia A and inhibitors to factor VIII (FVIII). b) people with severe hemophilia A without inhibitors to FVIII.		
Dosage form	Strength	EML	EMLc
Injection	12 mg/0.4 mL in vial	No	Yes
	30 mg/mL in vial	No	Yes
	60 mg/0.4 mL in vial	Yes	Yes
	105 mg/0.7 mL in vial	Yes	No
	150 mg/mL in vial	Yes	No
	300 mg/2 mL in vial	Yes	No

Emicizumab has been licensed for the treatment of PwHA of any age starting from birth. The safety and efficacy of the drug in infants and children has been reported in clinical trials (HAVEN 2, HOHOEMI, HAVEN 7) and through real-world experience. Target population: 3

Emicizumab is delivered subcutaneously according to the licensed dosing schedule; this consists of a loading dose of 3 mg/kg once weekly for 4 weeks, followed by a maintenance dose of either 1.5 mg/kg/week, 3 mg/kg every 14 days, or 6 mg/kg/month. These different dosing regimens are interchangeable, and the availability of different vial sizes (vials containing 30 mg/ml in a 1 ml vial; vials containing 150 mg/ml in a 0,4, 0,7, or 1 ml vial) allows for flexible adaptation to the possible treatment schedules.

Dose and dose flexibility: 3

Patient acceptability 0-5 years: 3

Patient acceptability 6-12 years: 3

Excipient safety: 3

Emicizumab is already in liquid form, and is ready to be transferred into a syringe and injected subcutaneously without the need for further manipulation. Administration considerations: 3

Emicizumab requires refrigerated storage but has no bulky/heavy packaging and has a less than 2-year shelf-life. Stability, storage conditions, primary packaging material: 1-2

Registration status: 3

Section 5: Listing as an individual medicine or as representative of a pharmacological class or therapeutic group (square box listing)

This submission relates to the listing of individual medicine. No other medicine of this type, a bispecific factor IXa- and factor X-directed antibody that functions as a FVIII mimetic, is currently approved in any jurisdiction.

Section 6: Information supporting the public health relevance

Proposed listing

1. People of all ages with all severities of hemophilia A and inhibitors FVIII
2. People of all ages with severe hemophilia A without inhibitors to FVIII

Epidemiological data

The prevalence at birth per 100,000 males is estimated to be 24.6 cases for all severities of hemophilia A, 9.5 cases for severe hemophilia A, 5.0 cases for all severities of hemophilia B, and 1.5 cases for severe hemophilia B *(1)*. According to the prevalence at birth estimates and based on the world population in 2024 *(2)*, the expected number of people born with hemophilia is 1,213,600, of whom 451,000 should have severe hemophilia.

The prevalence at birth is similar world-wide; however, survival to adulthood, especially among severely affected patients, is lower in low- and middle-income countries (LMICs) with restricted access to efficacious coagulation therapies *(1)*. Eighty percent (80%) of the expected PwH have been identified in Europe; with approximately 9% in Africa, 17% in South-East Asia, 27% in the Western Pacific, 47% in the Eastern Mediterranean, and 58% in the Americas *(6)*. Identification of patients is close to 100% in Canada and the U.S., but lower in Latin America *(7)*.

FVIII inhibitors occur in approximately 30% of PwHA who receive factor concentrates. Most patients develop an inhibitor within a median of 9–12 exposure days to FVIII. The overall inhibitor prevalence for all severities and all PwHA is 5-7% and for severe disease 12-13% *(6)*.

Alternative medicines (2023 WHO Model List of Essential Medicines)

<u>Core List</u>

Cryoprecipitate, pathogen-reduced

Cryoprecipitate, not pathogen-reduced (therapeutic alternative)

<u>Complementary List</u>

Coagulation FVIII

Section 7: Treatment details

INDICATIONS AND USAGE *(8)*

Emicizumab is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients, ages newborn and older, with hemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors.

DOSAGE AND ADMINISTRATION *(8)*

Recommended Dosage

The recommended loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of:

- 1.5 mg/kg once every week, or
- 3 mg/kg once every two weeks, or
- 6 mg/kg once every four weeks.

The selection of a maintenance dose should be based on healthcare provider guidance with consideration of regimens that may increase patient adherence. Administration of the FVIII mimetic is less frequent and less invasive than intravenous (IV) administration of FVIII, resulting in a decreased burden on people with hemophilia and the healthcare system. There are no age and/or weight restrictions.

The prophylactic use of bypassing agents should be discontinued the day before starting emicizumab. prophylaxis.

The prophylactic use of FVIII products may be continued during the first week of emicizumab prophylaxis.

If a dose of emicizumab is missed, administer the dose as soon as possible and then resume the usual dosing schedule. Do not administer two doses on the same day to make up for a missed dose.

Laboratory monitoring of emicizumab is unnecessary for routine prophylaxis, decreasing the burden on the person with hemophilia and the health care system. When non-adherence is suspected, activated partial thromboplastin clotting time (aPTT) test can be used.

Preparation and Administration

Emicizumab is intended for use under the guidance of a healthcare provider. After proper training in subcutaneous injection technique, a person with hemophilia may self-inject, or their caregiver may administer emicizumab. Self-administration is not recommended for children less than 7 years of age.

A syringe, a transfer needle with a filter, and an injection needle are needed complete the administration.

CONTRAINDICATIONS *(8)*

None.

BLACK BOX WARNING: THROMBOTIC MICROANGIOPATHY AND THROMBOEMBOLISM *(8)*

Cases of thrombotic microangiopathy (TMA) and thrombotic events (TEs) 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 emicizumab prophylaxis. If aPCC is administered, monitor for the development of TMA and TEs. Discontinue aPCC and suspend dosing of emicizumab if symptoms occur.

PwHA and inhibitors can control bleeding with bypass agents (either aPCCs or Factor VIIa). An individual who has inhibitors and is using emicizumab should avoid aPCCs for breakthrough bleeding or surgery and instead use Factor VIIa, another bypass agent, which can be used safely without risk of thromboses.

IMMUNOGENICITY *(8)*

Treatment with emicizumab may induce anti-drug antibodies. Anti-emicizumab antibodies were reported in 5.1% of patients (34/668) treated with emicizumab in clinical trials. Most patients with anti-emicizumab-kxwh antibodies did not experience a change in emicizumab plasma concentrations or an increase in bleeding events; however, in uncommon cases (incidence < 1%), the presence of neutralizing antibodies with decreasing plasma concentration may be associated with loss of efficacy. Monitor for clinical signs of loss of efficacy (e.g., increase in breakthrough bleeding events) and if observed, promptly assess the etiology and consider a change in treatment if neutralizing anti-emicizumab-kxwh antibodies are suspected.

LABORATORY COAGULATION TEST INTERFERENCE

Emicizumab affects intrinsic pathway clotting-based laboratory tests, including activated clotting time (ACT), activated partial thromboplastin time (aPTT), and all assays based on aPTT, such as the one-stage FVIII activity. Therefore, intrinsic pathway clotting-based laboratory test results in patients treated with emicizumab should not be used to monitor emicizumab activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titers. The chromogenic assay provides an accurate measurement of FVIII replacement when needed.

Section 8: Review of evidence for benefits and harms

Search Methodology: Literature search

A comprehensive literature search was performed using PubMed/MEDLINE from 1 January 2017 to the cut-off date of 12 July 2024. The year of 2017 was selected because it was when the first phase 3 study on emicizumab was published. A combination of indexing and free text terms for hemophilia A and emicizumab were used for the search strategy. Studies were included if reporting original primary data, registry data, or real-world evidence from PwHA receiving emicizumab. All ages and disease severities were included. Any type of study was included (clinical trials, registries, and other types of real-world data studies, such as observational studies, claims database reports, and e-health records). To fulfil the inclusion criteria, publications must have been in English language. Studies that reported on *in vitro* models, animal models, cell lines, and other molecules were excluded.

The full literature search data set included 319 articles, including 57 publications where the manufacturer, Roche, is mentioned in the affiliations or as the funder of the study. This literature search also contains articles that mention registries of interest in the title, abstract, affiliations or keywords columns (American Thrombosis and Hemostasis Network, PedNet Haemophilia Registry, Canadian Bleeding Disorders Registry, FranceCoag, HemNet, and the United Kingdom Haemophilia Centre Doctors' Organisation National Haemophilia Database).

In addition, the WFH reviewed abstract books for the 2023 and 2024 International Society of Haemostasis and Thrombosis (ISTH) Congresses, the 2024 World Federation of Hemophilia (WFH) Congress, the 2023 American Society of Hematology (ASH) Congress, and the 2023 and 2024 European Association of Haemophilia and Allied Disorders Congresses.

An additional on-line search was conducted for articles related to cost-effectiveness, which found 15 articles related to use in patients with inhibitors and six articles related to patients without inhibitors.

Systematic literature reviews (SLR) and meta-analyses (MA) focusing on emicizumab was also conducted (see Part 4).

Key health outcomes:

- Reduction in annual bleed rate (ABR)
- Reduction in annual joint bleed rate (AJBR)
- Reduction in annual rate of treated bleeds (ATBR)
- Reduction in number of target joints (a target joint is defined as three bleeds in same joint in less than 6 months)
- Improvement in joint health scores as measured by the Hemophilia Joint Health Score (HJHS) tool
- Percentage of patients with zero annual bleeding events
- Improved health-related outcomes and quality of life outcomes
- Survival

Comparative effectiveness and comparative safety

Part 1 – Studies in people with hemophilia A of any age or severity and inhibitors to FVIII

Comparators, alternative treatments

- Prophylactic treatment with bypassing agents—recombinant FVIIa and/or activated prothrombin complex concentrate—to prevent bleeding (12)

- On-demand treatment with bypassing agents—recombinant FVIIa and/or activated prothrombin complex concentrate—to stop active bleeding (12)
- Immune tolerance induction with multiple weekly infusions over many months to years of plasma-derived or recombinant FVIII to tolerize patient to FVIII

N.B. Cryoprecipitate and pathogen-reduced cryoprecipitate was never the comparator in clinical trials because they are not recommended in hemophilia management guidelines *(3)* and such a study would not receive ethics approval.

Key research findings

In PwHA and inhibitors to FVIII, emicizumab prophylaxis has been shown to:

- Dramatically reduce bleeding events compared to prophylaxis or on-demand treatment with bypassing agents in infants, children, adolescents, and adults.
- Reduce consumption of bypassing agents in surgical situations.
- Improve joint health.
- Be safe and well-tolerated.
- Have an extremely low immunogenicity rate (less than 1% neutralizing anti-drug antibodies).
- Be associated with meaningful improvements in health-related outcomes and quality of life.
- Reduce caregiver burden.

Studies

Emicizumab Prophylaxis in Hemophilia A with Inhibitors (HAVEN 1) *(4)*

Results from the HAVEN 1, a pivotal phase 3, open-label, multicenter, randomized trial of 109 males 12 years and old with hemophilia A with a prior history of inhibitors, were published in the New England Journal of Medicine in 2017. The reported ABR was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) for participants who received emicizumab prophylaxis (N=35) compared to 23.3 events (95% CI, 12.3 to 43.9) in participants who had no prophylaxis (N=18). This represented an 87% reduction in ABR that significantly favored emicizumab prophylaxis (P<0.001). Among the 24 participants who had previously received prophylactic treatment with bypassing agents, emicizumab prophylaxis resulted in a 79% reduction in ABR (P<0.001). The AEs of TMA (2 participants) and TEs (two participants) were reported in participants who had received multiple infusions of aPCC for breakthrough bleeding. These AEs led to the Federal Drug Administration (FDA) black box warning in the product label regarding the concomitant use of emicizumab and aPCC. Researchers concluded that subcutaneous emicizumab prophylaxis administered once weekly or every 2 weeks led to a significantly lower bleeding rate than no prophylaxis. More than half the participants who received emicizumab prophylaxis had no treated bleeding events during the study. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous FVIII prophylaxis.

A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors *(9)*

Results from the phase 3, open-label, non-randomized HAVEN 2 study were published in Blood in 2019. A total of 88 male PwH were enrolled, with a median age of 7 years, and 85 participants were <12 years of age. The median duration of the efficacy period of the trial was 58 weeks of treatment. In participants receiving emicizumab once a week (n = 65), the ABR was 0.3 (95% CI, 0.17-0.50), and 77% had no treated bleeding events. An intraindividual comparison of 15 participants who previously took bypassing agent prophylaxis showed that emicizumab prophylaxis reduced the ABR by 99% (95% CI, 97.4-99.4). In participants receiving emicizumab every 2 weeks (n = 10) the ABR was 0.2 (95% CI, 0.03-1.72). In participants receiving emicizumab every four weeks (N=10), the ABR was 2.2 (95% CI, 0.69-6.81). Two of the 88 participants developed antidrug antibodies (ADAs) with neutralizing potential; one experienced loss of efficacy, and in the other ADAs disappeared

over time without intervention or breakthrough bleeding. Researchers concluded that emicizumab prophylaxis has been shown to be a highly effective novel medication for children with hemophilia A and inhibitors.

The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study *(10)*

The HAVEN 1 study was a pivotal phase 3, open-label, multicenter, randomized trial of 109 males 12 years and old with hemophilia A with a prior history of inhibitors *(4)*. A follow-up on health-related outcomes was published in Haemophilia in 2019, which showed that participants on emicizumab prophylaxis missed fewer workdays and were hospitalized less than those not on emicizumab prophylaxis. They concluded that in PwHA with inhibitors, emicizumab prophylaxis was associated with substantial and meaningful improvements in health-related outcomes.

Safety analysis of rFVIIa with emicizumab dosing in congenital hemophilia A with inhibitors: Experience from the HAVEN clinical program *(11)*

This paper, published in the Journal of Thrombosis and Haemostasis in 2019, included data from the HAVEN1 (109 males 12 years and older), HAVEN2 (85 males, 12 years and less) and HAVEN4 (41 males, 12 years and older). The authors show that there were no serious AEs, no TMAs, or TEs deemed to be associated with rFVIIa when used for breakthrough bleeding in conjunction with emicizumab prophylaxis. Researchers concluded that rFVIIa use in the context of emicizumab prophylaxis does not change the rFVIIa safety profile as described in the product information.

Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study *(12)*

This phase 3, multicentre, open-label, two-stage study, included participants aged 12 years and older with severe congenital haemophilia A or haemophilia A with FVIII inhibitors. A total of 41 adults and adolescents with hemophilia A and FVIII inhibitors given emicizumab once every 4 weeks for 24 weeks. The ABTR was 2.4 (95% CI 1.4-4.3). Twenty-three (56.1%; 95% CI 39.7-71.5) of 41 reported no treated bleeds and 37 (90%; 76.9-97.3) reported zero to three treated bleeds. No TEs or development of de-novo antidrug antibodies with neutralising potential or FVIII inhibitors were observed. The researchers concluded that emicizumab, given once every 4 weeks, showed clinically meaningful bleed control while being well tolerated and that this regimen could improve patient care by decreasing treatment burden and increasing adherence to effective prophylaxis, potentially decreasing the development of bleeding sequelae for PwHA.

Health-related quality of life and caregiver burden of emicizumab in children with haemophilia A and factor VIII inhibitors-Results from the HAVEN 2 study *(13)*

This study examined the results from the HAVEN2 study and was published in Paediatric Blood Cancer to measure health-related quality of life and caregiver burden, children aged 8 to 11 used the Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form. Caregivers of children aged 0 to 11 years used the Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden. The results showed that prophylactic emicizumab was accompanied by substantial and sustained improvements in Health-Related Quality of Life (HRQoL) of pediatric PwHA with FVIII inhibitors and their caregivers.

Safety and efficacy of long-term emicizumab prophylaxis in hemophilia A with factor VIII inhibitors: A phase 3b, multicenter, single-arm study (STASEY) *(14)*

In this phase 3b study, published in Research and Practice in Thrombosis and Haemostasis in 2022, researchers assessed the safety of emicizumab prophylaxis, including incidence and severity of AEs and AEs of special interest (TEs and

thrombotic microangiopathies). Secondary objectives included assessing ABRs. Overall, 195 participants were enrolled and 193 received emicizumab. The median (range) duration of exposure was 103.1 (1.1-108.3) weeks. Seven (3.6%) participants discontinued emicizumab. The most common AEs were arthralgia (*n* = 33, 17.1%) and nasopharyngitis (*n* = 30, 15.5%). The most common treatment-related AE was injection-site reaction (*n* = 19, 9.8%). Two fatalities were reported (polytrauma with fatal head injuries and abdominal compartment syndrome); both were deemed unrelated to emicizumab by study investigators. Two TEs occurred (myocardial infarction and localized clot following tooth extraction), that were also deemed unrelated to emicizumab. The ABR for treated bleeds was 0.5 (95% CI, 0.27-0.89). Overall, 161 participants (82.6%) had zero treated bleeds. Researchers concluded that the safety profile of emicizumab prophylaxis was confirmed in a large population of PwHA with FVIII inhibitors and no new safety signals occurred. The majority of participants had zero treated bleeds.

Emicizumab prophylaxis in haemophilia A with inhibitors: Three years follow-up from the UK Haemophilia Centre Doctors' Organisation (UKHCDO) *(15)*

This study, published in Hemophilia in 2023, was evaluated the safety, bleeding outcomes, and early effects on joint health of emicizumab prophylaxis in a large, unselected cohort using national registry and patient reported Haemtrack (HT) data between 01 January 2018 and 30 September 2021. The UK National Haemophilia Database (NHD) prospectively analyzed bleeding outcomes in people with ≥6 months emicizumab HT data and compared results with previous treatment, if available. The analysis included 117 PwHA and FVIII inhibitors. The mean ABR was 0.32 (95% CI, 0.18-0.39) over a median 42 months treatment with emicizumab. Within-person comparison (n = 74) demonstrated an 89% reduction in ABR after switching to emicizumab and an increase in zero treated bleed rate from 45 to 88% ($p < .01$). In a subgroup of 37 people, total Hemophilia Joint Health Scores improved in 36%, remained stable in 46%, and deteriorated in 18%, with a median (IQR) within-person change of -2.0 (-9, 1.5) ($p = .04$). Post-approval adverse event reporting identified three arterial TEs, two were considered possibly drug-related. Other AEs were generally non-severe and usually limited to early treatment. These included cutaneous reactions (3.6%), headaches (1.4%), nausea (2.8%) and arthralgia (1.4%). Researchers concluded that emicizumab prophylaxis is associated with sustained low bleeding rates and was generally well-tolerated in PwHA and inhibitors. These real-world results support results obtained from clinical trials.

Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value: Final Evidence Report of the Institute for Clinical and Effectiveness Review in th e United States *(16)*

The Institute for Clinical and Effectiveness Review (ICER) in the United States published a report on the treatment of patients with hemophilia A and inhibitors in 2018. ICER concluded that:

1. Prophylactic emicizumab provides a net health benefit compared with no prophylactic therapy for patients less than 12 years of age.
2. Prophylactic emicizumab provides a net health benefit compared with no prophylactic therapy for patients more than 12 years of age.
3. Prophylactic emicizumab provides net health benefits compared with prophylactic therapy with bypassing agents (BPAs) for patients less than 12 years of age.
4. Prophylactic emicizumab provides net health benefits compared with prophylactic therapy with bypassing agents (BPAs) for patients more than 12 years of age.
5. Prophylactic emicizumab offers other health benefits:
    a. reduced complexity that will significantly improve health outcomes
    b. significantly reduced caregiver or family burden
    c. significant impact on improving return to work and/or overall productivity.

Part 2 – Studies in people with severe hemophilia A without inhibitors

Comparators, alternative treatments

- Prophylactic treatment with FVIII concentrates—plasma-derived or recombinant—to prevent bleeding
- On-demand treatment with FVIII concentrates—plasma-derived or recombinant—to stop active bleeding (Note that WFH Guidelines for Management of Hemophilia and consensus recommendations of the European Directorate for Quality of Medicines and Healthcare *(17)* recommend prophylaxis over on-demand treatment. In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. (See Section 9.)

N.B. Cryoprecipitate—pathogen-reduced or not—is never the comparator in clinical trials as cryoprecipitate is not recommended in guidelines and such a study would not receive ethics approval.

Key research findings

In people with severe hemophilia A without inhibitors to FVIII, emicizumab prophylaxis has been shown to:

- Dramatically reduce bleeding events compared to on-demand FVIII treatment in infants, children, adolescents and adults.
- Significantly reduce bleeding events compared to FVIII prophylaxis in infants, children, adolescents and adults.
- Reduce consumption of FVIII in surgical situations.
- Result in clinically relevant improvements in joint scores in younger PwHA and those with target joints ~~after~~ 48 weeks of emicizumab and maintain bone/joint health during 72 weeks of emicizumab prophylaxis.
- Be safe and well tolerated.
- Have an extremely low immunogenicity rate (less than 1% neutralizing anti-drug antibodies).
- Be associated with meaningful improvements in health-related outcomes and quality of life.
- Reduce caregiver burden.

Studies

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors *(18)*

This phase 3, open-label, multicenter, randomized study (HAVEN 3) enrolled 152 adults and adolescents aged 12 years and older without FVIII inhibitors. The ABR in participants who received emicizumab prophylaxis once-a week-was 1.5, and once-every-two weeks was 1.3. In participants who had previously been on FVIII prophylaxis, the ABR was reduced by 68**%** (P<0.001)**.** In those who had previously been on on-demand (episodic) FVIII treatment, ABR decreased by 96% P<0.001. More than half the participants who received prophylaxis had no treated bleeding events. There were no TEs or TMAs, was no development of antidrug antibodies, and no new development of FVIII inhibitors. Researchers concluded that emicizumab prophylaxis administered once weekly or every 2 weeks led to a significantly lower bleeding rate than no prophylaxis among PwHA without inhibitors. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous FVIII prophylaxis.

Long-term outcomes with emicizumab in hemophilia A without inhibitors: results from the HAVEN 3 and 4 studies *(19)*

In a paper published in Research Practices in Thrombosis and Hemostasis in 2024**,** researchers evaluated the long-term efficacy and safety of emicizumab prophylaxis in PwHA without FVIII inhibitors with data from the phase 3 HAVEN 3 (151 participants) and HAVEN 4 (40 participants) studies. Participants received emicizumab maintenance doses of 1.5 mg/kg every week or 3 mg/kg every 2 weeks (HAVEN 3), or 6 mg/kg every 4 weeks (HAVEN 4). At the last study visit the median (range) duration of emicizumab exposure was 248.1 (6.1-287.1*)* weeks. The mean ABTR was 2.0 (95% CI, 0.23-7.15) for

weeks 1 to 24, which decreased to 0.9 (95% CI, 0.01-5.28) by weeks 217 to 240. Overall, 98.4% participants experienced ≥1 AE, with 185 treatment-related AEs in 37.2% participants. Forty-four (23.0%) participants reported a serious AE. Two TEs were reported, which were deemed unrelated to emicizumab by the investigator. No thrombotic microangiopathies were reported. Researchers concluded that with nearly 5 years of emicizumab exposure there was sustained bleed control with no new safety signals observed during long-term follow-up.

Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5) *(20)*

In a randomized study published in Research and Practices in Thrombosis and Haemostasis in 2022, researchers found that in 70 patients across the Asia-Pacific region, emicizumab 1.5 mg/kg once weekly and 6 mg/kg every 4 weeks demonstrated bleed control in this study population, was well tolerated, and could improve use of prophylaxis in PwHA.

Effect of emicizumab prophylaxis on bone and joint health markers in PwHA without factor VIII inhibitors in the HAVEN 3 study *(21)*

A follow-on analysis of the HAVEN 3 study was published in Haemophilia in 2022. Haemophilia Joint Health Score (HJHS) from baseline was evaluated in 117 PwHA without FVIII inhibitors who were previously on FVIII prophylaxis. The HJHS scores were lower in PwHA who were previously on FVIII prophylaxis, PwHA who were <40 years of age, and those that had no target joints at baseline, than those who were not receiving no prophylaxis, >40 years of age, or had target joints at baseline. The researchers concluded that additional data were needed to understand the long-term affects on bone and joint health, especially in those who start emicizumab at a young age.

Part 3 – Studies in PwHA with and without inhibitors

Key research findings

See Parts 1 and 2.

Studies

Emicizumab prophylaxis in infants with hemophilia A (HAVEN 7): primary analysis of a phase 3b open-label trial *(22)*

HAVEN 7 (NCT04431726) was a phase 3b, multicenter, open label, single-arm trial of emicizumab in infants with severe hemophilia A without FVIII inhibitors. It is the first clinical trial dedicated to infants and was designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in this young population. Participants received emicizumab 3 mg/kg maintenance dose every 2 weeks for 52 weeks and are continuing emicizumab during the 7-year long-term follow-up. A total of 55 male participants received emicizumab (median treatment duration: 100.3; range, 52-118 weeks). Median age at enrollment was 4.0 months (range, 9 days to 11 months 30 days). The ABTR was 0.4 (95% CI, 0.30-0.63), with 54.5% of participants (n = 30) having zero treated bleeds. No intracranial hemorrages occurred. All 42 treated bleeds in 25 participants (45.5%) were traumatic. Nine participants (16.4%) had ≥1 emicizumab-related AE (all grade 1 injection-site reactions). No AE led to treatment changes and no deaths, TEs, or TMAs occurred. No participant tested positive for ADAs. Two participants were confirmed positive for FVIII inhibitors. This primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe HA without FVIII inhibitors.

Surgical outcomes in people with hemophilia A taking emicizumab prophylaxis: experience from the HAVEN 1-4 studies *(23)*

In a paper published in Blood Advances in 2022, researchers pooled data from the HAVEN 1-4 phase 3 clinical trials to provide a summary of all minor and major surgeries in PwHA with or without FVIII inhibitors who were receiving

emicizumab prophylaxis. Overall, 233 surgeries were carried out during the HAVEN 1-4 trials, including 18 major surgeries (including arthroplasty and synovectomy) in 18 PwHA (10 with FVIII inhibitors) and 215 minor surgeries (including minor dental and joint procedures, central venous access device placement or removal, and endoscopies) in 115 PwHA (64 with FVIII inhibitors). The treating physician determined what, if any perioperative hemostatic support was required. Overall, the median age was 33.5 (IQR, 13.0-49.0) years and the median emicizumab exposure time before surgery was 278.0 (IQR, 177.0-431.0) days. One-hundred and forty-one (141, 65.6%) of the minor surgeries were managed without additional prophylactic factor concentrate, and of those, 121 (85.8%) were not associated with a postoperative bleed. Fifteen (15, 83.3%) of the major surgeries were managed with additional prophylactic factor concentrate and 12 of 15 (80.0%) were associated with no intraoperative or postoperative bleeds. These data demonstrate that minor and major surgeries can be performed safely in PwHA receiving emicizumab prophylaxis.

Low immunogenicity of emicizumab in persons with haemophilia A *(24)*

In a paper published in Hemophilia in 2021, researchers reported on 668 PwHA in 7 completed or ongoing phase 3 studies for emicizumab. Thirty-four (34, 5.1%) developed anti-drug antibodies (ADAs) after exposure to emicizumab. ADAs were transient and resolved on their own in 14 (41.2%) instances. In vitro analysis showed that ADAs were neutralising in 18 cases (52.9%) and associated with decreased emicizumab concentration in 4 (11.7%); of those, one discontinued emicizumab due to loss of efficacy. Researchers concluded that the immunogenicity risk of emicizumab in phase 3 studies was low. ADAs, including in vitro neutralising ADAs, were not associated with a change in safety profile. Routine surveillance is, therefore, not warranted; however, in cases where a loss and/or waning of efficacy are observed, prompt evaluation by a healthcare provider should be sought.

Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies *(25)*

In a paper published in Blood in 2021, researchers reviewed results from 401 pediatric and adult patients, with and without FVIII inhibitors, from the phase 3 HAVEN 1, 2, 3 and 4 studies. Across a median efficacy period of 120.4 weeks, the ABR was 1.4 (95% CI, 1.1-1.7). In an analysis of 24-week treatment intervals, ABRs declined and then stabilized at <1; at weeks 121 to 144 (n = 170), the mean ABTR was 0.7 (95% CI, 0-5.0). During weeks 121 to 144, 82.4% of participants had 0 treated bleeds, 97.6% had ≤3 treated bleeds, and 94.1% reported no treated target joint bleeds. Bleeding into target joints decreased substantially. No participant discontinued the trials because of AEs beyond the 5 previously described in the individual references (3 TMAs and 2 TEs, all associated with aPCC use). This study included 970.3 patient-years of exposure, demonstrating that emicizumab prophylaxis maintained low bleed rates in PwHA of all ages with andwithout FVIII inhibitors. Emiczumab remains well tolerated and no new safety concerns were identified.

Emicizumab prophylaxis: Prospective longitudinal real-world follow-up and monitoring *(26)*

In a paper published in Hemophilia in 2021, researchers reported real-world prospective results from 107 patients, including 58 children, on emicizumab prophylaxis. Twenty-nine percent (31/107) had inhibitors. PwHA were followed for a median of 67 weeks. Fifty-three (53) PwHA experienced zero bleeds. Among children, most bleeds (94%) were trauma-related, whereas 61% of adults sustained at least one spontaneous joint bleed. Four (4) patients experienced major bleeds. A major bleed that co-presented with central venous line thrombosis was fatal one infant. No other serious AEs were encountered. Seven patients decided to stop emicizumab treatment for various reasons. Researchers concluded that emicizumab prophylaxis was mostly well tolerated, although 50% of patients experienced breakthrough bleeds.

Bleeding control improves after switching to emicizumab: Real-world experience of 177 children in the PedNet registry *(27)*

In a paper published in Hemophilia in 2024, researchers extracted data from the multicentre prospective observational PedNet Registry (NCT02979119). Inclusion criteria for extraction included children with hemophilia A and ≥50 FVIII exposures or inhibitors who were receiving prophylactic emicizumab therapy. A total of 177 patients started emicizumab at a median of 8.6 years (IQR 4.8–13.1); 64% had no FVIII inhibitors. The follow up period before emicizumab was 1.68 years (IQR 1.24–1.90) and during prophylaxis with emicizumab was 1.32 years (IQR 0.94–2.11). In PwHA without inhibitors, the mean ABR was reduced after starting emicizumab from 2.41 (CI 1.98–2.95) to 1.11 (CI .90–1.36, $p < .001$), and the AJBR decreased from 0.74 (CI 0.56–0.98) to 0.31 (CI 0.21–0.46, $p < .001$). In PwHA with inhibitors, the mean ABR decreased from 5.08 (CI 4.08–6.38) to 0.75 (CI 0.56–1.01, $p < .001$) after starting emicizumab prophylaxis, and the AJBR decreased from 1.90 (CI 1.42–2.58) to 0.34 (CI .21–.56, $p < .001$). Five (3%) emicizumab-related AEs were reported, including one patient with ADAs. Researchers concluded that the study showed improved bleeding control compared to previous treatment and a favorable safety profile during real-world emicizumab therapy in pediatric PwHA.

Non-replacement therapy for hemophilia in low-income countries: experience from a prospective study in Ivory Coast *(28)*

This prospective study evaluated the impact of prophylaxis with emicizumab among male children with severe hemophilia A from the Ivory Coast. A total of 33 Pw severe HA, 2 to 13 years of age, with and without inhibitors. Bleeds, factor replacement consumption, quality of life, and satisfaction of the patients and their parents were assessed. Overall, at one year after initiating emicizumab, participants averaged a 99% reduction in bleeding rates, with an increase from 18% to 100% of participants having zero spontaneous joint bleeds. Three (3) required a single FVIII infusion following a traumatic bleed. Health-related quality of life measures significantly improved, and perception of treatment efficacy was positively rated by children and parents. Acceptance, tolerance, and adherence were excellent. Emicizumab was instrumental in successfully implementing uninterrupted, highly efficacious, and well-tolerated prophylaxis in 72% of the Ivorian children with severe hemophilia A. These data illustrate how innovative and disruptive non-replacement therapies can be. Emicizumab has the potential to provide equity in care by profoundly and rapidly modifying hemophilia burden, with a magnified impact in low-income countries.

Emicizumab state-of-the-art update *(29)*

In a supplement article published in Haemophilia in 2022, researchers reported on the evolving real-world experience in using emicizumab, they stated, “Emicizumab has confirmed its safety, efficacy and pharmacokinetic profile in paediatric, adolescent and adult patients receiving emicizumab at various prophylactic dosing regimens. The emicizumab current global rollout includes over 100 countries with 29 low to middle-income countries accessing emicizumab through the World Federation of Hemophilia (WFH) Humanitarian Aid Program. The diversity of emicizumab dosing and pharmacokinetic tools such as the Calibra® and the WAPPS-Hemo platforms make it possible to achieve prophylaxis goals in line with the WFH Hemophilia treatment guidelines recommendations, with minimal drug wastage. The emerging experience from long-term clinical trials and long-term real-world follow-up confirm the safety, efficacy, and pharmacokinetic profile of emicizumab in paediatric haemophilia A patients. A few questions, including inhibitor recurrence, concurrent use of emicizumab with various replacement therapies and inhibitor eradication, are being addressed through multiple ongoing clinical studies. The current global rollout of emicizumab is remarkable, and versatile dosing regimens and evolving pharmacokinetic tools such as the Calibra® and WAPPS-Hemo platforms make it a treatment choice available also for pharmacokinetic guided personalised treatment. Data from paediatric studies are consistent with those seen in adolescent and adult Haemophilia A.”

Part 4. Systemic literature reviews and meta-analyses

Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B *(30)*

In this meta analysis, researchers searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, electronic databases, conference proceedings, and reference lists to identify relevant articles and reviews. Six rancomized clinical trials (totaling 397 males aged 12 to 75 years) were eligible for inclusion. The clinical effects, economic effects, patient-reported outcomes, and adverse events of prophylaxis of emicizumab and other non-clotting factor therapies in clinical trials were compared with prophylaxis with clotting factor therapies, bypassing agents, placebo, or no prophylaxis. This meta-analysis found that emicizumab reduced the ABR for all bleeds, treated bleeds, and spontaneous bleeds (moderate-certainty evidence). However, emicizumab did not significantly reduce the ABR for joint and target joint bleeds compared to on-demand therapy. Prophylaxis with emicizumab resulted in an 11.3-fold increase in the proportion of patients with no bleeds. Quality of life outcomes measured using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) showed improvement in the physical and total health scores (low certainty of evidence). The risk of serious adverse events in participants without inhibitors also did not differ following prophylaxis with emicizumab versus on-demand therapy (moderate-certainty evidence).

Emicizumab prophylaxis in people with hemophilia A and inhibitors: a systematic review and meta-analysis *(31)*

This systematic literature review and meta-analysis searched the CENTRAL, MEDLINE, Scopus, and LILACS databases on February 21, 2023 for publications that evaluated the bleeding endpoints between PwHA with inhibitors using prophylaxis with emicizumab or bypassing agents. Five publications (including 56 PwHA with inhibitors) were selected from the 543 retrieved records. Overall, bleeding endpoints were lower with emicizumab prophylaxis than prophylaxis with bypassing agents. All the publications had at least one risk of bias. The only common parameter for the meta-analysis was the ABTR. During emicizumab prophylaxis, the ABTR was lower than during BPA prophylaxis (standard mean difference: -1.58; 95% confidence interval -2.50, -0.66, P = 0.0008; I2 = 68.4%, P = 0.0031). The authors concluded that emicizumab was superior to BPA for prophylaxic management of hemophilia A with inhibitors. Both the small population size and potential risk of bias should be considered when evaluating these results.

Efficacy/effectiveness and safety of emicizumab prophylaxis of people with hemophilia A: a systematic review and meta-analysis *(32)*

A systematic review was conducted evaluating the efficacy/effectiveness and the safety of emicizumab as prophylaxis for PwHA compared to prophylaxis with factor VIII (FVIII) or bypassing agents in patients without and with inhibitors, respectively. A database-directed search was performed in August 2022 and then updated in March 2023. Eleven studies were selected by two independent reviewers. The ABRs for total treated bleeding events were evaluated by meta-analysis. The standard mean differences for ABR were -0.6 (95%CI -1.0 to -0.2, p-value = 0.0002), among PwHA without inhibitors (compared with FVIII), and -1.7 (95%CI -2.4 to -0.9, p-value <0.00001), among PwHA with inhibitors (compared with bypassing agents). There was moderate heterogeneity in both meta-analyses. The most frequent adverse event was injection site reaction. The authors concluded that prophylaxis with emicizumab was superior in reducing the ABR compared to prophylaxis with FVIII or BPA.

Section 9: Summary of recommendations in current clinical guidelines

Recommendations in existing WHO guidelines

None.

Recommendations in other current clinical guidelines

<u>WFH Guidelines for the Management of Hemophilia, 3rd edition *(3)*</u>

For Recommendations on people with inhibitors, See Chapter 8: Inhibtors to Clotting Factors, Section: Therapeutic options for FVIII inhibitor patients (pages 98-100) (this section is copied *verbatim*)

- "The factor substitution therapy, emicizumab, is increasingly used to prevent hemorrhage in FVIII inhibitor patients. This agent is effective for preventing bleeds (prophylaxis) in hemophilia A inhibitor patients but is not indicated for treating bleeds. Thus, breakthrough bleeds require treatment with FVIII CFCs (for low-responding inhibitors) as described above, or hemostatic bypassing agents (for high-responding inhibitors), as described below. (page 98-99)

Emicizumab

- The factor substitution therapy, emicizumab, a bispecific monoclonal antibody and FVIII mimic, has been licensed for bleed prevention in patients with hemophilia A with and without inhibitors. Patients on emicizumab who experience breakthrough bleeds require episodic treatment with FVIII CFCs or with hemostatic bypassing agents, as described above. (page 99)
- Several phase 3 clinical trials and post-marketing experience have shown that emicizumab is effective prophylaxis in adults and children with inhibitors. As emicizumab is injected subcutaneously every 1, 2, or 4 weeks, the burden of prophylaxis is much less than with bypassing agents. Emicizumab reduces morbidity, complications, and hospitalization, and is cost-effective.
- Prophylaxis dosing with emicizumab consists of an induction period of 3.0 mg/kg/week for 4 weeks by subcutaneous injection. This is followed thereafter by 1.5 mg/kg/week or alternative dosing schedules including 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.

    As emicizumab interferes with the measurement of FVIII:C and FVIII inhibitors using the one-stage FVIII assay, a specific chromogenic assay using bovine reagents is used to detect inhibitors to FVIII. (page 99)

Recommendation 8.3.5:

For patients with hemophilia A and inhibitors who receive emicizumab, the WFH recommends bovine chromogenic assays (bovine FX in kit reagent) to monitor inhibitor levels.

- Close monitoring of clinical response to emicizumab and laboratory monitoring of inhibitor titer level is advised with a chromogenic Bethesda assay using bovine reagents.
- In patients receiving emicizumab who have risk factors for thrombosis, e.g., past venous thromboembolism, obesity, smoking, chronic infection, or inflammation, rFVIIa should be used with caution due to the potential risk of acute non-STEMI and pulmonary embolism.

Recommendation 8.3.6:

For patients with hemophilia A and inhibitors receiving emicizumab, the WFH recommends close clinical monitoring for thrombosis, adverse reactions, and thrombotic microangiopathy.

REMARK: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.

Recommendation 8.3.7:
As emicizumab is used to prevent, but not treat, acute bleeds in patients with hemophilia A and inhibitors, the WFH recommends clotting factor replacement therapy for acute bleeds.

Recommendation 8.3.8:
For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH recommends clotting factor replacement therapy including FVIII for those with low-responding inhibitors; the WFH prefers rFVIIa over aPCC for those with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy.

REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.

Recommendation 8.3.9:
For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH prefers rFVIIa over aPCC, because of the risk of thrombotic microangiopathy.

REMARK : The WFH suggests following black box warnings for emicizumab and maintaining vigilance as new evidence develops."

Recommendation 8.3.19:
For patients with severe hemophilia A and inhibitors, the WFH recommends emicizumab over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis.

<u>For guidelines on Severe hemophilia A without inhibitors See Chapter 6: Prophylaxis in Hemophilia (pages 72; this section is copied *verbatim*)</u>

- Prophylaxis in hemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding, especially joint hemorrhages, which would lead to arthropathy and disability. Prophylaxis should enable people with hemophilia to lead healthy and active lives including participation in most physical and social activities (at home, school, work, and in the community), similar to the non-hemophilic population.
- Prophylaxis with clotting factor concentrates (CFCs) is referred to as regular replacement therapy; it stands in contrast to episodic replacement therapy (also known as on-demand therapy), which is defined as the administration of CFCs only at the time of a bleed. Episodic therapy, regardless of the doses used, while essential in reducing the pain and debilitating impact of individual bleeds, does not alter the bleeding profile significantly and hence does not change the natural history of hemophilia leading to musculoskeletal damage and other complications due to bleeding.
- Therefore, the use of prophylaxis is always recommended over episodic therapy. In countries with healthcare constraints and for patients with limited access to CFCs, less intensive prophylaxis regimens may be used. Still, in all countries the ideal is for patients to not experience any bleeds (i.e., achieve "zero" bleeds).
- With the advent of innovative non-factor replacement therapies, which for the most part can be administered subcutaneously, prophylaxis is being redefined as the regular administration (intravenously, subcutaneously, or otherwise) of a hemostatic agent/agents to enhance hemostasis and effectively prevent bleeding in people with hemophilia.

Recommendation 6.1.1:

For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.

REMARK: In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used.

Section 6.5 | Prophylaxis with non- factor replacement therapy (page 77)

- Note: Emicizumab is the only licensed non-factor replacement product available at the time of publication.
- The development of new non-factor hemostatic therapies in hemophilia is causing a reconsideration of the concepts and definitions of prophylaxis. These new non-factor therapies include emicizumab, a FVIII mimetic already in clinical use for hemophilia A, and others still in development including agents that inhibit natural endogenous anticoagulants (antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C).
- Emicizumab and those non-factor agents in development differ from conventional types of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously, and in some cases can be administered as infrequently as once every 2 or 4 weeks. Additionally, these agents are not associated with the peak and trough curves of protection that we now see with factor prophylaxis regimens.
- There have already been extensive clinical trials of emicizumab in patients with hemophilia A with and without inhibitors that attest to the safety and bleed protection with this agent. (For emicizumab use in patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)
- Emicizumab is already making it easier to start patients on prophylaxis at an earlier age and without the need for CVADs. This may cause a re-evaluation of what constitutes primary prophylaxis, as perhaps prophylaxis can be commenced much earlier than usual. This could reduce the risk of bleeding that now occurs in very young children (ages 6-12 months) prior to the usual commencement of prophylaxis.
- Non-factor products should allow for less burdensome prophylaxis, which might improve adherence and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (including those with moderate hemophilia), permitting them increased participation in social and sports activities. The above is already demonstrated by the increasing uptake and usage of emicizumab.
- All of these developments are transforming the concepts of prophylactic intensity. No longer can one refer to high-dose prophylaxis as prophylaxis that results in factor trough levels of 1%-3%.

Recommendation 6.5.1:

For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.

Section 10: Summary of available data on comparative cost and cost-effectiveness

Comparative cost and cost-effectiveness must be analyzed for each of the two indications for emicizumab: 1) patients with inhibitors, where the comparators are bypassing agents such as rFVIIa and/or activated prothrombin complex concentrate, administered either prophylactically or episodically for active bleeding, and FVIII replacement therapy in a regimen of immune tolerance induction, and 2) PwHA without inhibitors where the comparator is FVIII replacement therapy administered either prophylactically or episodically for active bleeding.

It must again be noted, as seen in the previous section on current clinical guidelines, that in severe hemophilia, episodic treatment is not recommended. Only prophylaxis is effective in changing the natural history of hemophilia and preventing musculoskeletal damage and other complications due to bleeding.

The costs of emicizumab and its comparators vary widely from country to country. As a result, comparative cost, budget impact, and cost-effectiveness must be analyzed country-by-country.

Indication 1 – Studies in people with hemophilia A and inhibitors to FVIII

Key research findings

All studies discovered through the literature search show cost savings for emicizumab compared to bypassing agents in PwHA with inhibitors. This has been demonstrated in Malaysia, Iran, Korea, India, Brazil, Italy, France, Peru, Spain, South Africa, United States, Canada, Portugal and Turkey. No study indicated the contrary. See a summaries of each study below.

Budget Impact of Emicizumab for Routine Prophylaxis of Bleeding Episodes in Patients With Hemophilia A With Inhibitors *(33)*

"A budget impact model was built to assess the cost implication of introducing emicizumab for routine prophylaxis of bleeding episodes in PwHA with inhibitors. The model was based on the public healthcare system in Malaysia over a 5-year duration." "The primary analysis computed healthcare costs for emicizumab compared with no prophylactic regimen to calculate the budget needed to treat all patients with hemophilia A with inhibitors." "The introduction of emicizumab as prophylaxis decreased healthcare use costs by US$2 821393. The total emicizumab cost to treat 20 pediatric patients and 40 adults in 2021 was US$7 738 518." Sensitivity analysis determined that emicizumab was cost saving if the ABR was 16 with no prophylactic regimen, but not when the ABR was 6. The conclusion was that the 5-year budget impact might be considered reasonable and possibly cost-saving, depending on the ABR.

A Comparison Between on Demand Usage of rFVIIa vs Prophylaxis Use of Emicizumab in High Titer Inhibitory Hemophilia A Patients in Iran; A Cost Utility Analysis *(34)*

Treatment of Hemophilia is extremely expensive, especially for high titer inhibitory patients. The current standard of care in Iran primarily involves on demand usage of bypassing agents (BPAs) like rFVIIa. This study evaluated the cost-effectiveness of emicizumab compared with rFVIIa in PwHA with inhibitors. A lifetime Markov model with societal perspective was run for patients with different ages and different ABRs. Clinical efficacy, safety, route of administration, and dosage considerations were extrapolated from the literature for both emicizumab and rFVIIa. Clinical management practice in Iran was obtained from clinician interviews and audit data from Mofid Hospital. Costs calculated based on official local tariff prices and utilities were taken from publications. Age dependent weight and adjusted life table were used. One-way deterministic sensitivity analysis and budget impact analysis were performed. Emicizumab remained dominant in all scenarios. The study concluded that emicizumab prophylaxis is a dominant choice for Iranian inhibitor hemophilia patients with ABR of 16 and above with considerable cost saving.

Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea *(35)*

This cost-utility analysis was published in Haemophilia in 2021. They first report that in Korea PwHA with inhibitors experience frequent spontaneous bleeding, approximately once a week, and require expensive bypassing agent treatments to control bleeding over their lifetime. The study used a "lifetime Markov model with health states of 'alive with bleeds' and 'dead', and simulated the experience of patients with inhibitors receiving emicizumab prophylaxis (treatment arm) or on demand bypassing agents (control arm) and estimated expected clinical and economic outcomes under each treatment arm." The model included parameters for comparative effectiveness, clinical and epidemiologic characteristics of Korean patients, costs of drug treatment and medical events, and utility for 'alive with bleeds' state under each treatment. They utilized local data, including National Health Insurance claims data, national statistics, literature and expert surveys with haematologists. The "base-case analysis results showed that compared with on demand bypassing agents, lifetime emicizumab prophylaxis prevented 807 bleeding events, extended 3.04 quality-adjusted life-years and reduced costs by 2.6 million US dollars." Therefore, emicizumab prophylaxis was the dominant treatment option, with better effectiveness and lower overall costs than bypassing agents and on demand treatment. A series of one-way sensitivity analyses consistently showed dominant results for prophylaxis with emicizumab.

Budget impact and cost-utility analysis of prophylactic emicizumab versus on-demand bypassing agents for adolescent severe haemophilia A patients with inhibitors in India *(36)*

This cost-utility analysis had had two aims: first to evaluate the cost-utility of emicizumab compared to traditional bypassing agents in the treatment of severe hemophilia A patients with inhibitors in India; secondary to analyze the budgetary impact of introducing emicizumab for this patient population from the perspective of the public health system in India. In india, people with severe hemophilia A with inhibitors are currently being treated with bypassing agents like activated prothrombin complex concentrates (aPCC) and recombinant factor VIIa. In this study, a Markov model was created to compare the prophylactic emicizumab therapy against bypassing agents for a hypothetical cohort of 10-year-old adolescents in India. Cost-utility was expressed as costs (in US dollars) per quality-adjusted life-years (QALYs) gained. Prophylactic emicizumab was a cost saving intervention when compared to current practices .

Cost-Effectiveness Analysis of Emicizumab Versus Bypassing Agents in Patients With Hemophilia A with Inhibitors in The Brazilian Public Healthcare System Perspective *(37)*

A 2019 Brazilian study evaluated the cost-effectiveness of emicizumab versus bypassing agents in the Brazilian Public Healthcare System (SUS) and the work was presented at the 2019 ISPOR conference. "A probabilistic two state transition (Alive with hemophilia A and inhibitors vs Death) Markov model was populated using treated bleed rates and utilities from HAVEN 1 trial. The study cohort was composed of male patients two years old at diagnosis and followed in a lifetime horizon. General population mortality was adjusted by disease severity… Direct medical costs included drug acquisition, arthroplasty, hospitalization and AE management." Result validity was evaluated with sensitivity analyses. Overall, emicizumab prophylaxis improved Quality Adjusted Life Years (QALY) and averted 273 bleed events, with a cost decrease of 661,000 USD, and was dominant over prophylaxis with bypassing agents. Emicizumab also averted 405 bleeding events with an incremental cost-effective ratio of $7,842 USD compared to on demand bypassing agents. The result was driven mostly by the reduction in breakthrough bleed costs and utility. The authors conclude that once-weekly subcutaneous emicizumab prophylaxis was dominant over intravenous prophylaxis with bypassing agents in treating PwHA with inhibitors, offering higher effectiveness and lower costs.

Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with Inhibitors in Italy (33) *(38)*

A study published in 2019 in *Coagulation and Fibrinolysis* assessed the cost-effectiveness of emicizumab prophylaxis compared with BPA prophylaxis and its possible budget impact from the Italian National Health Service (NHS) perspective. "A Markov model and a budget impact model were developed to estimate the cost-effectiveness and budget impact of emicizumab prophylaxis in PwHA with inhibitors. The model was populated using treatment efficacy from clinical trials and key clinical, cost and epidemiological data retrieved through an extensive literature review. Compared with BPAs prophylaxis, emicizumab prophylaxis was found to be more effective (0.94 quality adjusted life years) and cost saving (–€19.4/–€24.4million per patient lifetime) in a cohort of 4-year-old patients with HA and inhibitors who failed immune tolerance induction. In the probabilistic sensitivity analysis, emicizumab prophylaxis had always 100% probability of being cost-effective at any threshold. Further, the use of emicizumab prophylaxis was associated to an overall budget reduction of €45.4 million in the next 3 years." The authors conclude that emicizumab prophylaxis can be considered a cost-saving treatment for PwHA with inhibitors and that emicizumab treatment is also associated with a significant reduction of the health care budget, making this new treatment a sustainable and convenient health care option for Italian NHS.

Cost-Effectiveness of Emicizumab Versus Bypassing Agents in Patients with Haemophilia A and FVIII Inhibitors In France *(39)*

In a paper published in Haemophilia in 2021, researchers evaluated the cost-effectiveness of emicizumab compared to the current management by BPAs in France. The analysis was based on a Markov model with two health states over a 5-year time period. Emicizumab was compared with BPAs (aPCC and rFVIIa) in prophylaxis or on-demand, according to their real-life use in the FranceCoag Network cohort (RFC). "The ICER is expressed in euros per QALY (Quality-Adjusted Life Year). Bleeding rates are derived from the HAVEN 1 clinical trial for emicizumab and BPA on-demand, and an indirect comparison for BPA prophylaxis. Quality of life data are derived from the HAVEN 1 trial. The costs of treatment, AEs and hospitalizations were included. Various sensitivity analyses were performed to evaluate the uncertainty around the result." Emicizumab prophylaxis was a dominant strategy: it was more effective and less costly than BPAs. Over 5 years, the mean total cost per patient was 2,3 MV in patients treated with emicizumab, versus 2,6 MV with BPA, associated to 3,3 and2,4 QALYs respectively. Thus, emicizumab brings 0,9 additional QALYs per patient for a saving of 283 642V. Sensitivty analysis of uncertaintaies did not alter the results. The authors conclude that emicizumab is cost-effect compared to BPA in France. The methodology used was accepted by the Economic and Public Health Evaluation Committee (*Commission d'évaluation économique et de santé* – CEESP) in its Opinion of October 9, 2018. The limitations of this analysis are mainly based on the lack of data to model the consequences of the reduction of bleeding on the long-term evolution of arthropathy and disability.

Cost-effectiveness study of prophylaxis with emicizumab versus bypassing agents in patients with severe hemophilia A in Peru *(40)*

In a study published in Medwave in 2022, researchers performed a cost-effectiveness study of emicizumab prophylaxis for children and adults with severe hemophilia A compared with the current disease management in the Peruvian Ministry of Health and Social Security Health Insurance. The patient transition between medical states was modeled with Markov methodology, and the lifetime costs and incremental effects of emicizumab compared to current management were estimated. The budgetary impact of emicizumab was estimated by projecting annual net costs and its five-year present value. In the Ministry of Health, emicizumab would generate savings between 14.6 and 16.0 per child and 11.8 per adult, in current US$ million. Social Security Health Insurance savings would be 12.8 to 14.9 per child and 40.1 per adult. In addition, this strategy would generate effectiveness gains, measured in quality-adjusted life-years, of 0.36 per child and 0.56 per adult and 0.25 per child, and 0.36 per adult in those respective institutions. The budgetary impact would be a net annual saving of 12.8 and 15.0 US$ million in those entities. The authors concluded that the current management of

hemophilia A is very costly and has health outcomes inferior to those possible with emicizumab. Emicizumab would produce significant savings and better patient health.

Costs of the management of hemophilia A with inhibitors in Spain *(41)*

A study published in Global and Regional Health Technology Assessment in 2021 aimed to estimate the direct and indirect costs of the management of hemophilia A with inhibitors, in adult and pediatric patients, including the prophylaxis with emicizumab. Researchers calculated the costs of the on-demand and prophylactic treatments with bypassing agents and emicizumab prophylaxis over 1 year. The study considered direct healthcare costs (drugs, visits, tests, and hospitalizations), direct non-healthcare costs (informal caregivers), and indirect costs (productivity loss). The results showed that the "annual costs of the prophylactic treatment per patient varied between €543,062.99 and €821,415.77 for adults, and €182,764.43 and €319,826.59 for children, while on-demand treatment was between €532,706.84 and €789,341.91 in adults, and between €167,523.05 and €238,304.71 in pediatric patients. In relation to other prophylactic therapies, emicizumab showed the lowest costs, with up to a 34% and 43% reduction in the management cost of adult and pediatric patients, respectively. It reduced the bleeding events and administration costs," as this drug is administered less frequently and through subcutaneous injection rather than intravenously. Emicizumab prophylaxis also decreased the cost of other healthcare resources such as visits, tests, and hospitalizations, as well as indirect costs. The authors conclude that prophylaxis with emicizumab reduced direct and indirect costs, resulting in cost savings for the National Health System and society.

Evaluating the cost and intermediary cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A with inhibitors in South Africa *(42)*

An analysis was conducted by the Health Economics and Epidemiology Research Office (HE2RO) at the University of Witwatersrand in South Africa, with no interests pertaining to emicizumab, to evaluate the cost and budget impact per annum of treating bleeds in patients with hemophilia A with inhibitors. They evaluated two arms: 1) patients receiving emicizumab prophylaxis and their treatment of bleeds using bypassing agents, and 2) a comparator arm of on-demand treatment of bleeds only with bypassing agents (i.e. no prophylaxis). "The average cost per patient year is lower in the emicizumab arm for ABR of 4 bleeds per annum (Scenario 1), 6 bleeds per annum (Scenario 2), 16 bleeds per annum (Scenario 3) and 12 bleeds per annum (Scenario 4)." "In Scenarios 1,2 and 4, treating patients with hemophilia A with inhibitors is cost-saving ranging between saving R94.4 million to R352 million per year, depending on the number of cases, the ABR, and the treatment of bleeds strategy. In Scenario 3, which replicates current cost of procurement of bypassing agents in the comparator arm, the incremental cost per bleed averted is estimated at R84,594."

Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value: Final Evidence Report of the Institute for Clinical and Effectiveness Review in the United States *(16)*

The Institute for Clinical and Effectiveness Review in the United States conducted an independent cost analysis for the treatment of PwHA and inhibitors in 2018. ICER concluded that "emicizumab prophylaxis resulted in fewer bleed events, equal life years, increased QALYs, and lower costs compared to both no prophylaxis and BPA prophylaxis. For patients aged 12 years or older, emicizumab prophylaxis was estimated to avoid a total of 606 bleeds over a lifetime compared to no prophylaxis and 114 compared to BPA prophylaxis, while QALYs gained were 0.91 and 0.20 versus no prophylaxis and BPA prophylaxis, respectively. For patients under the age of 12 years, the expected reduction in bleeds over a lifetime was 1,091 compared to no prophylaxis and 217 compared to BPA prophylaxis, with respective QALY gains of 2.39 and 0.38. Lifetime incremental costs of emicizumab prophylaxis were approximately $8.9 million lower compared to no prophylaxis and $71 million lower compared to BPA prophylaxis for patients aged 12 years or over. For a patient population starting

the model under 12 years of age, the lifetime incremental costs of emicizumab were $10 million lower compared to no prophylaxis and $78.5 million lower for emicizumab versus BPA prophylaxis."

Emicizumab: Economic Review Report: CADTH TECHNOLOGY REVIEW *(43)*

In 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) conducted an evaluation of emicizumab. The report concluded, "CADTH reanalysis of the Budget Impact Analysis (BIA) used up-to-date (2017) figures for population prevalence and market shares, and estimated cost savings of $32,920,731 (in year 1, and slightly higher in subsequent years) after making emicizumab available in the inhibitor population. In summary, in the inhibitor population, emicizumab is the dominant treatment compared with BPA prophylaxis … The cost-effectiveness of emicizumab in the non-inhibitor population remains unknown. CADTH estimated that reimbursing emicizumab in patients with hemophilia A with inhibitors will result in cost savings."

News from ISPOR: economics of emicizumab evaluated *(44)*

This article highlights a selection of pharmacoeconomic studies on emicizumab that were presented at the 22nd Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) which was held in November 2019 in Copenhagen, Denmark. The studies showed emicizumab to be cost-effective for the treatment of hemophilia A with inhibitors in France, Italy, Portugal and Turkey.

Part 2 – Studies in people with hemophilia A without inhibitors to FVIII

Key research findings

The cost savings and cost-effectiveness show more variability for the treatment of people with severe hemophilia A without inhibitors. Results vary by country. Studies show cost savings and cost-effectiveness with emicizumab compared to FVIII in India and the United States, but not in Europe and the United Kingdom. See studies below.

Cost-effectiveness analysis of emicizumab prophylaxis in patients with haemophilia A in India *(45)*

This study, published in Haemophilia in 2023, assessed the economic evaluation of emicizumab treatment for non-inhibitor severe hemophilia A (HA) patients in India. "A Markov model evaluated the cost-effectiveness of emicizumab prophylaxis compared to on-demand therapy (ODT), low-dose prophylaxis (LDP; 1565 IU/kg/year), intermediate-dose prophylaxis (IDP; 3915 IU/kg/year) and high-dose prophylaxis (HDP; 7125 IU/kg/year) PwHA without FVIII inhibitors. Inputs from HAVEN-1 and HAVEN-3 trials included transition probabilities of different bleeding types. Costs and benefits were discounted at a 3.5% annual rate… In the base-case analysis, emicizumab was cost-effective compared to HDP, with an incremental cost-effectiveness ratio (ICER) per quality-adjusted life-years (QALY) of Indian rupees (INR) 27,869. Compared to IDP, ODT and LDP, emicizumab prophylaxis could be considered a cost-effective option if the paying threshold is >1 per capita gross domestic product (GDP) with ICER/QALY values of INR 264,592, INR 255,876 and INR 305,398, respectively. One-way sensitivity analysis (OWSA) highlighted emicizumab cost as the parameter with the greatest impact on ICERs. Probabilistic sensitivity analysis (PSA) indicated that emicizumab had a 94.7% and 49.4% probability of being cost-effective at willingness-to-pay (WTP) thresholds of three and two-times per capita GDP." The authors concluded that emicizumab prophylaxis is cost-effective compared to HDP and provides value for money compared to ODT, IDP, and LDP for people with severe hemophilia A without inhibitors in India. Emicizumab has long-term humanistic, clinical, and economic benefits that outweigh the alternative options, which makes it a valuable choice in resource-constrained settings.

Model of Short- and Long-Term Outcomes of Emicizumab Prophylaxis Treatment for Persons with Hemophilia A *(46)*

A study published in the Journal of Managed Care and Specialty Pharmacy in 2020 developed an economic model to predict the short- and long-term clinical and economic outcomes of prophylaxis with emicizumab versus short-acting recombinant FVIII among persons with HA in the United States. "A Markov model compared clinical outcomes and costs of emicizumab versus FVIII prophylaxis among persons with severe HA from U.S. payer and societal perspectives. Patients started prophylaxis at age 1 year in the base case. Mutually exclusive health states considered were "no arthropathy," "arthropathy," "surgery," and "death." Serious AEs, breakthrough bleeds, and inhibitor development were simulated throughout the modeled time horizon. In addition to the prophylaxis drug costs, patients could incur other direct costs related to breakthrough bleeds treatment, serious AEs, development of inhibitors, arthropathy, and orthopedic surgery. Indirect costs associated with productivity loss (i.e., missed work or disabilities) were applied for adults. Model inputs were obtained from the HAVEN 3 trial, published literature, and expert opinion. The model used a lifetime horizon, and results for 1 year and 5 years were also reported. Deterministic sensitivity analyses and scenario analyses were conducted to assess robustness of the model. Over a lifetime horizon, the cumulative number of all treated bleeds and joint bleeds avoided on emicizumab versus FVIII prophylaxis were 278.2 and 151.7, respectively. Correspondingly, arthropathy (mean age at onset: 12.9 vs. 5.4 years) and FVIII inhibitor development (mean age at development: 13.9 vs. 1.1 years) were delayed. Total direct and indirect costs were lower for emicizumab versus FVIII prophylaxis for all modeled time horizons ($97,159 vs. $331,610 at 1 year; $603,146 vs. $1,459,496 at 5 years; and $15,238,072 vs. $22,820,281 over a lifetime horizon). The sensitivity analyses indicated that clinical outcomes were sensitive to efficacy inputs, while economic outcomes were driven by the discount rate, dosing schedules, and treatments after inhibitor development. Results for moderate to severe patients were consistent with findings in the severe HA population. The model suggests that emicizumab prophylaxis confers additional clinical benefits, resulting in a lower number of bleeding events and delayed onset of arthropathy and inhibitor development across all time assessment horizons. Compared with short-acting recombinant FVIII, emicizumab prophylaxis leads to superior patient outcomes and cost savings from U.S. payer and societal perspectives."

Cost-Effectiveness of Emicizumab Vs Efanesoctocog Alfa, Standard Half Life (SHL) and Other Extended Half Life (EHL) FVIII Products for Prophylaxis in People with Severe Hemophilia A without Inhibitors *(47)*

An analysis conducted in the U.S. and published in Blood in 2023 estimated the relative cost-effectiveness of these prophylactic therapies for PwHA, including the newly approved ultra extended half-life FVIII, efanesoctocog alfa. "A Markov model was developed with four FVIII-based health states (normal clotting function, mild hemophilia, moderate hemophilia, severe hemophilia) and death to compare emicizumab, efanesoctocog alfa, standard half-life (SHL) and other extended half-life (EHL) FVIII products as prophylaxis for PwHA in the United States (US). Advate and Eloctate data were used to represent SHL and EHL, respectively. The model considered a cohort of 38-year-old hemophilia A patients with average weight of 94.4 kg treated with prophylaxis. Probability of experiencing each health state was based on each product's pharmacokinetic data, where FVIII activity levels were used to determine disease severity. Other clinical inputs, including annualized bleed rates and AE risks, were estimated from clinical trial data. Wholesale acquisition cost (WAC) of drugs and healthcare costs of bleed management and AEs were included and were estimated from published literature. Utilities by disease severity were derived from published real-world health-related quality of life studies for hemophilia patients. Disutility of infusion was obtained from the published literature. Costs (in 2023 US dollars), quality-adjusted life-year (QALY), and total bleeds were estimated over a lifetime horizon. Cost-effectiveness was estimated as incremental cost per QALY gained. One-way and probabilistic sensitivity analyses were conducted. Over a lifetime, emicizumab was estimated to be less costly (total cost at $17.0 million for emicizumab vs $24.0 million, $19.3 million, and $18.2 million for efanesoctocog alfa, SHL, and EHL) and more effective (18.61 vs 18.58, 16.91, and 17.33 QALY) compared with efanesoctocog alfa, SHL, and EHL FVIII, respectively. Although efanesoctocog led to fewer bleeds (26.58 vs 59.91 bleeds over a lifetime), PwHA on emicizumab were expected to incur fewer bleeds (59.91 vs 198.45, and 108.58 bleeds) compared

with EHL and SHL. Results were robust to one-way and probabilistic sensitivity analyses. Findings in this cost-effectiveness analysis suggest that emicizumab is less costly and more effective (i.e., dominant) over a lifetime compared with available FVIII prophylaxis in pediatrics and adult PwHA in the US."

Cost-minimization analysis of recombinant factor VIII Fc versus emicizumab for treating patients with hemophilia A without inhibitors in Europe *(48)*

In an original research article published in the Journal of Medical Economics in 2022, researchers developed a cost-minimization model to compare recombinant extended half-life FVIII (rFVIIIFc) and emicizumab as prophylaxis for hemophilia A without inhibitors. "The model was based on 100 patients from the healthcare payer perspective in the UK, France, Italy, Spain, and Germany (5-year time horizon). Costs included: drug acquisition; emicizumab wastage by bodyweight (manufacturer's dosing recommendations); and additional FVIII for breakthrough bleeds. Scenario analyses (UK only): reduced emicizumab dosing frequency; and emicizumab maximum wastage. Total incremental 5-year savings for rFVIIIFc rather than emicizumab use range from 89,320,131 euros to 149,990,408 euros in adolescents/adults (12 years) and 173,417,486 euros to 253,240,465 euros in children (<12 years). Emicizumab wastage accounts for 6% of its total cost in adolescents/adults and 26% in children. Reducing the emicizumab dosing frequency reduces the incremental cost savings with rFVIIIFc, but these remain substantial (adolescents/adults, >92 million euros; children >32 million euros). Maximum emicizumab wastage increases by 86% and 106%, respectively, increasing the incremental cost savings with rFVIIIFc to 125,352,125 euros and 105,872,727 euros, respectively. Based on cost-minimization modeling, rFVIIIFc use for hemophilia A prophylaxis in patients without inhibitors is associated with substantial cost savings in Europe, reflecting not only higher acquisition costs of emicizumab, but also other costs including wastage related to available vial sizes."

N.B. Since the introduction of emicizumab, clinicians have developed strategies to completely eliminate wastage and respect dosing principles. This involves slightly adjusting the interval between treatments so as to inject the full vial without affecting drug levels or efficacy. On-line tools have been developed to aid clinicians.

Cost-effectiveness of recombinant factor VIII Fc versus emicizumab for prophylaxis in adults and adolescents with hemophilia A without inhibitors in the UK *(49)*

In an original research article published in the European Journal of Hematology in 2022, a cost-effectiveness model was developed to compare prophylactic treatment with extended half-life FVIII (rFVIIIFc) versus emicizumab in PwHA without inhibitors in the UK. The cost-effectiveness model was "based on a matching-adjusted indirect comparison and included male patients, aged ≥12 years, with hemophilia A without inhibitors. The model was designed as a Markov process with a flexible lifelong time horizon, and cost-effectiveness was presented as an incremental cost-effectiveness ratio. Base-case analysis and sensitivity analyses…were performed using the following treatment strategies: individualized prophylaxis with rFVIIIFc and prophylaxis with emicizumab administered once weekly (scenario analyses used regimens of once every 2 weeks or once every 4 weeks)." "Base-case analysis indicated that rFVIIIFc individualized prophylaxis was the dominant treatment strategy, with lower costs, a greater number of quality-adjusted life years, and a lower number of bleeds." The study concluded that rFVIIIFc has "proven efficacy and is cost-effective compared with emicizumab, providing clinicians with a viable treatment option to improve the health outcomes for adults and adolescents with hemophilia A in the UK."

Section 11: Regulatory status, market availability and pharmacopeia standards

Emicizumab was approved for treatment hemophilia A patients for with inhibitors (both pediatric and adult) by FDA on 17 November 2017 and European Medicines Agency (EMA) on 23 February 2018.

Emicizumab was approved for treatment of hemophilia A patients without inhibitors (both pediatric and adult) by the EMA on 4 October 2018 and by FDA on 11 March 2019.

To date, emicizumab has been approved for:

- **PwHA and with inhibitors to FVIII in 122 countries (shown in chronological order of approval)**

1. US
2-32. EU*
33. Australia
34. Japan
35. Georgia
36. Mauritius
37. Kuwait
38. UAE
39. Thailand
40. Brazil
41. Moldova
42. Canada
43. New Zealand
44. Taiwan
45. Ukraine
46. Dominican Republic
47. Cuba
48. Qatar
49. Chile
50. Oman
51. Russia
52. Hong Kong
53. Mexico
54. Paraguay
55. Albania
56. Switzerland
57. Singapore
58. El Salvador
59. China
60. Saudi Arabia
61. Isreal
62. Honduras
63. Korea
64. Jordan
65. Indonesia
66. Northern Macedonia
67. Panama
68. India
69. Colombia
70. Argentina
71. Macau
72. Namibia
73. Bosnia & Herzegovina
74. Zimbabwe
75. Aruba
76. Guatemala
77. Serbia
78. South Africa
79. Morocco
80. Malaysia
81. Costa Rica
82. Palestine
83. Trinidad & Tobago
84. Turkmenistan
85. Egypt
86. Curacao
87. Montenegro
88. Turkiye
89. Lebanon
90. Ecuador
91. Kazakhstan
92. Bolivia
93. Azerbaijan
94. Bahrain
95. Peru
96. Tanzania
97. Belarus
98. Sint Marteen
99. Vietnam
100. Philippines
101. Nicaragua
102. Ethiopia
103. Pakistan
104. Ghana
105. Guyana
106. Bangladesh
107. Uruguay
108. Botswana
109. Libya
110. Tunisia
111. Algeria
112. Iran
113. Ivory Coast
114. Iraq
115. Kosovo
116. Sudan
117. Kenya
118. Sri Lanka
119. Venezuela
120. Zambia
121. Nigeria
122. Kyrgyzstan

*EU: 28 member states plus three EEA countries: Norway, Iceland, and Lichtenstein.

- **People with severe hemophilia A and without inhibitors to FVIII in 112 countries (shown in chronological order of approval)**

1. US
2. UAE
3. Australia
4. Singapore
5. Mauritius
6. Georgia
7. Japan
8. Saudi Arabia
9. Chile
10. Brazil
11-41. EU*
42. New Zealand
43. Paraguay
44. Isreal
45. Cuba
46. Thailand
47. Dominican Republic
48. El Salvador
49. Canada
50. India
51. Mexico
52. Northern Macedonia
53. Honduras
54. Colombia
55. Albania
56. Argentina
57. Montenegro
58. Switzerland
59. Ukraine
60. Turkiye
61. Indonesia
62. Hong Kong
63. Ecuador
64. Serbia
65. Kazakhstan
66. Taiwan
67. Macau
68. Bolivia
69. Panama
70. Russia
71. Peru
72. Guatemala
73. Qatar
74. Malaysia
75. Lebanon
76. Turkmenistan
77. Oman
78. Egypt
79. Belarus
80. Morocco
81. Costa Rica
82. Sint Maarten
83. Kuwait
84. Korea
85. South Africa
86. Bahrain
87. Vietnam
88. Philippines
89. Jordan
90. Nicaragua
91. China
92. Guyana
93. Pakistan
94. Zimbabwe
95. Botswana
96. Uruguay
97. Namibia
98. Iraq
99. Bangladesh
100. Ivory Coast
101. Sudan
102. Libya
103. Trinidad & Tobago
104. Tunisia
105. Sri Lanka
106. Aruba
107. Venezuela
108. Curacao
109. Bosnia and Herzegovina
110. Azerbaijan
111. Kosovo
112. Nigeria

*EU: 28 member states plus three EEA countries: Norway, Iceland, and Lichtenstein.

- **People with mild and moderate hemophilia A and without inhibitors to FVIII in 50 countries (shown in chronological order of approval)**

1. Switzerland	35. Montenegro	39. Georgia	43. Panama	47. Thailand
2-32. EU*	36. Costa Rica	40. Russia	44. Indonesia	48. Algeria
33. Qatar	37. Oman	41. Moldova	45. Bahrain	49. Hong Kong
34. Paraguay	38. UK	42. Bolivia	46. Belarus	50. Kazakhstan

*EU: 28 member states plus three EEA countries: Norway, Iceland, and Lichtenstein.

There are no generics and/or biosimilars of emicizumab available on the market, nor any existing or planned licensing agreements with generic/biosimilar manufacturers and/or the Medicines Patent Pool. Emicizumab is not included on the WHO List of Prequalified Finished Pharmaceutical Products.

Pharmacopeia standards

Emicizumab is a monoclonal antibody. To our knowledge, there are no pharmacopeia standards available for emicizumab.

The United States Pharmacopeia Standards for monoclonal antibodies are available here:

https://www.usp.org/biologics/mabs

The International Pharmacopeia Guideline for the production and quality control of monoclonal antibodies and related products intended for medicinal use are available here:

https://www.who.int/publications/m/item/guideline-for-the-safe-production-and-quality-control-of-monoclonal-antibodies

European Directorate for the Quality of Medicines and HealthCare specifications are available here:

https://www.ema.europa.eu/en/development-production-characterisation-specifications-monoclonal-antibodies-related-products-scientific-guideline

British Pharmacopeia standards on Monoclonal Antibodies for Human Use are available here:

https://vnras.com/wp-content/uploads/pdf/British-Pharmacopoeia-2022-Vol-4.pdf

Section 12: References

1. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C et al. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019;171(8):540-6 (https://doi.org/10.7326/M19-1208).
2. United Nations (2024). World Population Prospects 2024: Summary of Results. UN DESA/POP/2024/TR/NO. 9. New York: United Nations. (https://desapublications.un.org/publications/world-population-prospects-2024-summary-results).
3. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158 (https://doi.org/10.1111/hae.14046).
4. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017;377(9):809-18 (https://doi.org/10.1056/NEJMoa1703068).
5. International Classification of Diseases 11th Revision. . (https://icd.who.int/en.).
6. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. Ther Adv Hematol. 2013;4(1):59-72 (https://doi.org/10.1177/2040620712464509).
7. World Federation of Hemophilia 2022 Annual Global Survey. (https://www1.wfh.org/publications/files/pdf-2399.pdf).
8. Roche (Genetech and Chugai). Federal Drug Administration (FDA). HEMLIBRA)emicizumab-kxwh). Federal Drug Administration (FDA). Revised January 2024. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761083s018lbl.pdf.).
9. Young G, Liesner R, Chang T, Sidonio R, Oldenburg J, Jimenez-Yuste V et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134(24):2127-38 (https://doi.org/10.1182/blood.2019001869).
10. Oldenburg J, Mahlangu JN, Bujan W, Trask P, Callaghan MU, Young G et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study. Haemophilia. 2019;25(1):33-44 (https://doi.org/10.1111/hae.13618).
11. Levy GG, Asikanius E, Kuebler P, Benchikh El Fegoun S, Esbjerg S, Seremetis S. Safety analysis of rFVIIa with emicizumab dosing in congenital hemophilia A with inhibitors: Experience from the HAVEN clinical program. J Thromb Haemost. 2019;17(9):1470-7 (https://doi.org/10.1111/jth.14491).
12. Pipe SW, Shima M, Lehle M, Shapiro A, Chebon S, Fukutake K et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019;6(6):e295-e305 (https://doi.org/10.1016/S2352-3026(19)30054-7).
13. Oldenburg J, Shima M, Kruse-Jarres R, Santagostino E, Mahlangu J, Lehle M et al. Outcomes in children with hemophilia A with inhibitors: Results from a noninterventional study. Pediatr Blood Cancer. 2020;67(10):e28474 (https://doi.org/10.1002/pbc.28474).
14. Jimenez-Yuste V, Peyvandi F, Klamroth R, Castaman G, Shanmukhaiah C, Rangarajan S et al. Safety and efficacy of long-term emicizumab prophylaxis in hemophilia A with factor VIII inhibitors: A phase 3b, multicenter, single-arm study (STASEY). Res Pract Thromb Haemost. 2022;6(8):e12837 (https://doi.org/10.1002/rth2.12837).
15. Wall C, Xiang H, Palmer B, Chalmers E, Chowdary P, Collins PW et al. Emicizumab prophylaxis in haemophilia A with inhibitors: Three years follow-up from the UK Haemophilia Centre Doctors' Organisation (UKHCDO). Haemophilia. 2023;29(3):743-52 (https://doi.org/10.1111/hae.14762).
16. Institute for Clinical and Economic Review (ICER). Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value: Final Evidence Report. April 16, 2018. . (https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia_Final_Evidence_Report_041618.pdf).
17. Peyvandi F, Berger K, Seitz R, Hilger A, Hecquet ML, Wierer M et al. Kreuth V initiative: European consensus proposals for treatment of hemophilia using standard products, extended half-life coagulation

factor concentrates and non-replacement therapies. Haematologica. 2020;105(8):2038-43 (https://doi.org/10.3324/haematol.2019.242735).
18. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018;379(9):811-22 (https://doi.org/10.1056/NEJMoa1803550).
19. Mahlangu J, Jimenez-Yuste V, Ventriglia G, Niggli M, Barlera S, Hermans C et al. Long-term outcomes with emicizumab in hemophilia A without inhibitors: results from the HAVEN 3 and 4 studies. Res Pract Thromb Haemost. 2024;8(2):102364 (https://doi.org/10.1016/j.rpth.2024.102364).
20. Yang R, Wang S, Wang X, Sun J, Chuansumrit A, Zhou J et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022;6(2):e12670 (https://doi.org/10.1002/rth2.12670).
21. Kiialainen A, Niggli M, Kempton CL, Castaman G, Chang T, Paz-Priel I et al. Effect of emicizumab prophylaxis on bone and joint health markers in people with haemophilia A without factor VIII inhibitors in the HAVEN 3 study. Haemophilia. 2022;28(6):1033-43 (https://doi.org/10.1111/hae.14642).
22. Pipe SW, Collins P, Dhalluin C, Kenet G, Schmitt C, Buri M et al. Emicizumab prophylaxis in infants with hemophilia A (HAVEN 7): primary analysis of a phase 3b open-label trial. Blood. 2024;143(14):1355-64 (https://doi.org/10.1182/blood.2023021832).
23. Kruse-Jarres R, Peyvandi F, Oldenburg J, Chang T, Chebon S, Doral MY et al. Surgical outcomes in people with hemophilia A taking emicizumab prophylaxis: experience from the HAVEN 1-4 studies. Blood Adv. 2022;6(24):6140-50 (https://doi.org/10.1182/bloodadvances.2022007458).
24. Schmitt C, Emrich T, Chebon S, Fernandez E, Petry C, Yoneyama K et al. Low immunogenicity of emicizumab in persons with haemophilia A. Haemophilia. 2021;27(6):984-92 (https://doi.org/10.1111/hae.14398).
25. Callaghan MU, Negrier C, Paz-Priel I, Chang T, Chebon S, Lehle M et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 2021;137(16):2231-42 (https://doi.org/10.1182/blood.2020009217).
26. Barg AA, Budnik I, Avishai E, Brutman-Barazani T, Bashari D, Misgav M et al. Emicizumab prophylaxis: Prospective longitudinal real-world follow-up and monitoring. Haemophilia. 2021;27(3):383-91 (https://doi.org/10.1111/hae.14318).
27. van der Zwet K, de Kovel M, Motwani J, van Geet C, Nolan B, Glosli H et al. Bleeding control improves after switching to emicizumab: Real-world experience of 177 children in the PedNet registry. Haemophilia. 2024;30(3):685-92 (https://doi.org/10.1111/hae.15015).
28. Lambert C, Meite N, Kouassi GK, Dohoma AS, Bognini Akou SA, Sanogo I et al. Nonreplacement therapy for hemophilia in low-income countries: experience from a prospective study in Ivory Coast. Res Pract Thromb Haemost. 2023;7(1):100033 (https://doi.org/10.1016/j.rpth.2022.100033).
29. Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. Haemophilia. 2022;28 Suppl 4(Suppl 4):103-10 (https://doi.org/10.1111/hae.14524).
30. Olasupo OO, Noronha N, Lowe MS, Ansel D, Bhatt M, Matino D. Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B. Cochrane Database Syst Rev. 2024;2(2):CD014544 (https://doi.org/10.1002/14651858.CD014544.pub2).
31. Prudente TP, Camelo RM, Guimaraes RA, Roberti M. Emicizumab prophylaxis in people with hemophilia A and inhibitors: a systematic review and meta-analysis. Sao Paulo Med J. 2024;142(5):e2023102 (https://doi.org/10.1590/1516-3180.2023.0102.R1.20022024).
32. Muniz RL, Camelo RM, Araujo MS, Barbosa MM, Guerra AA, Acurcio FA et al. Efficacy/effectiveness and safety of emicizumab prophylaxis of people with hemophilia A: a systematic review and meta-analysis. Expert Rev Hematol. 2023;16(12):1087-97 (https://doi.org/10.1080/17474086.2023.2293096).
33. Watanabe AH, Lee SWH, Chai-Adisaksopha C, Lim MY, Chaiyakunapruk N. Budget Impact of Emicizumab for Routine Prophylaxis of Bleeding Episodes in Patients With Hemophilia A With Inhibitors. Value Health Reg Issues. 2022;28:7-13 (https://doi.org/10.1016/j.vhri.2021.07.003).
34. Saiyarsarai P, Robabpour Derakhshan A, Khedmati J, Eshghi P, Seyedifar M. A comparison between on-demand usage of rFVIIa vs prophylaxis use of emicizumab in high titer inhibitory hemophilia A patients

in Iran: A cost-utility analysis. Medicine (Baltimore). 2021;100(40):e27303 (https://doi.org/10.1097/MD.0000000000027303).
35. Lee H, Cho H, Han JW, Kim AY, Park S, Lee M et al. Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea. Haemophilia. 2021;27(1):e12-e21 (https://doi.org/10.1111/hae.14143).
36. Krishnamoorthy Y, Govindan D, Kannan N, Majella MG, Hariharan VS, Valliappan V. Budget impact and cost-utility analysis of prophylactic emicizumab versus on-demand bypassing agents for adolescent severe haemophilia A patients with inhibitors in India. Heliyon. 2024;10(5):e27089 (https://doi.org/10.1016/j.heliyon.2024.e27089).
37. Souza P, Puopolo GR, Leme-Souza R. COST-EFFECTIVENESS ANALYSIS OF EMICIZUMAB VERSUS BYPASSING AGENTS IN PATIENTS WITH HEMOPHILIA A WITH INHIBITORS IN THE BRAZILIAN PUBLIC HEALTHCARE SYSTEM PERSPECTIVE. 2019 (https://ispor.confex.com/ispor/euro2019/meetingapp.cgi/Paper/97736).
38. Cortesi PA, Castaman G, Trifiro G, Creazzola SS, Improta G, Mazzaglia G et al. Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with Inhibitors. Thromb Haemost. 2020;120(2):216-28 (https://doi.org/10.1055/s-0039-3401822).
39. Polack B, Trossaert M, Cousin M, Baffert S, Pruvot A, Godard C. Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France. Haemophilia. 2021;27(1):e1-e11 (https://doi.org/10.1111/hae.14129).
40. Bitran R, Pena C, Arpon P, Loayza N, Salas K, Del Villar C et al. Estudio de costo-efectividad de profilaxis con emicizumab versus agentes hemostaticos alternativos en pacientes con hemofilia A grave en Peru. Cost-effectiveness study of prophylaxis with emicizumab versus bypassing agents in patients with severe hemophilia A in Peru. Medwave. 2022;22(2):e8703 (https://doi.org/10.5867/medwave.2022.02.002118).
41. Bonanad S, Alvarez MT, Nunez R, Poveda JL, Gil B, Ruiz-Beato E et al. Costs of the management of hemophilia A with inhibitors in Spain. Glob Reg Health Technol Assess. 2021;8:35-42 (https://doi.org/10.33393/grhta.2021.2234).
42. Jamieson L, Hongoro D. Evaluating the cost and intermediary cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A with inhibitors in South Africa. 2023 (https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-04/Emicizumab%20Prophylaxis%20impact_N_30%20November%202023_final.pdf).
43. Hemlibra (Emicizumab): Economic Review Report. Ottawa: CADTH; 2019 Sep. (CADTH Technology Review; no. 21). (https://www.cda-amc.ca/sites/default/files/hta-he/ob0005-emicizumab-eeconomic-report.pdf).
44. News from ISPOR: economics of emicizumab evaluated. (https://link.springer.com/article/10.1007/s40274-019-6412-6).
45. Seth T, John MJ, Chakrabarti P, Shanmukhaiah C, Verma SP, Radhakrishnan N et al. Cost-effectiveness analysis of emicizumab prophylaxis in patients with haemophilia A in India. Haemophilia. 2024;30(2):426-36 (https://doi.org/10.1111/hae.14921).
46. Zhou ZY, Raimundo K, Patel AM, Han S, Ji Y, Fang H et al. Model of Short- and Long-Term Outcomes of Emicizumab Prophylaxis Treatment for Persons with Hemophilia A. J Manag Care Spec Pharm. 2020;26(9):1109-20 (https://doi.org/10.18553/jmcp.2020.19406).
47. Curtis R, Decker-Palmer M, Wilson M, McDade C, Lin C-W, Wallick C et al. Cost-Effectiveness of Emicizumab Vs Efanesoctocog Alfa, Standard Half Life (SHL) and Other Extended Half Life (EHL) FVIII Products for Prophylaxis in People with Severe Hemophilia a without Inhibitors. 2023; 142(Supplement 1):5053 (https://doi.org/10.1182/blood-2023-181062).
48. Mancuso ME, Castaman G, Pochopien M, Aballea S, Drzewiecka A, Hakimi Z et al. Cost-minimization analysis of recombinant factor VIII Fc versus emicizumab for treating patients with hemophilia A without inhibitors in Europe. J Med Econ. 2022;25(1):1068-75 (https://doi.org/10.1080/13696998.2022.2115777).

49. Kragh N, Tytula A, Pochopien M, Aballea S, Toumi M, Hakimi Z et al. Cost-effectiveness of recombinant factor VIII Fc versus emicizumab for prophylaxis in adults and adolescents with haemophilia A without inhibitors in the UK. Eur J Haematol. 2023;110(3):262-70 (https://doi.org/10.1111/ejh.13901).

Appendices

Appendix 1: Letter from the WFH to the WHO Director of Health Products Policy and Standards, Dated November 2, 2023.

Dr Clive Ondari
Director
Health Products Policy and Standards
World Health Organization
Geneva, Switzerland

November 2, 2023

Subject: Inclusion of pathogen-reduced cryoprecipitate and non-pathogen-reduced cryoprecipitate in the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) in 2023

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Dear Dr. Ondari,

The World Federation of Hemophilia (WFH) is the only global non-governmental agency dedicated to assisting those with bleeding disorders worldwide and has been in official relations with the WHO as a Non-State Actor for over 50 years. The WFH has periodically published international guidelines for the management of hemophilia. The 3rd edition, published in 2020, has recognized the rapid technological advances and associated cost decreases for clotting factor concentrates (CFCs) and non-clotting factor products used by countries of all income levels this past decade (1). Clotting factor concentrates and Factor VIII mimetic bispecific antibodies are the treatments of choice for prophylaxis to prevent bleeding and CFCs are the standard of care for treatment of bleeding.

While WFH supports pathogen-reduced cryoprecipitate (PR-cryo) as a treatment of bleeding when CFCs are unavailable, it is not preferred since it poses a residual infectious risk, particularly for non-enveloped viruses (e.g. parvovirus, hepatitis A). Only under life or limb threatening circumstances, and in the absence of an alternative virally inactivated therapy, should non-pathogen-reduced cryoprecipitate be used, since in low-income/lower-middle-income countries (LIC/LMIC) endemic HIV, HCV, HBV and other pathogens exist and adequate screening is variable (i.e., nucleic acid testing, quality plasma programs). As an example, this is shown in a recent meta-analysis of the prevalence of infectious disease agents in African blood donors, where an overall prevalence of 2% is reported (2). This prevalence will definitely result in exposure to these agents in haemophilia A patients who are administered untreated cryoprecipitate, as shown by modelling studies (3, 4). It should be noted that in many LIC and LMIC, where resource constraints may prohibit Nucleic Acid Testing, the screening of blood for infectious disease agents is performed using relatively insensitive methodologies such as Rapid Detection Tests (RDTs), antigen tests etc (5), thus failing to minimize the serological window and leading to a high residual risk of transmission and viral load in donations, as reported by the World Health Organization (6).

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The WFH acknowledges the role of the WHO's EML as a tool for governments to use in determining their country formularies, accessing cost-effective solutions and leveraging WHO's influence in securing support for health care. Regrettably, the WHO's Expert Committee on Selection and Use of Essential Medicines has used outdated information on the treatment standards and costs for hemophilia A and B in their most recent changes to the EML (7). By placing PR-cryo on the most recent 2023 EML and EMLc as a core medication, with non-PR-cryo as a therapeutic alternative, relegating CFCs to the status of complementary medicines, while not considering recently emerged treatments such as Factor VIII mimetic bispecific antibodies, the committee has overlooked the WFH guidelines for the management of hemophilia, compiled by 50 hemophilia treaters worldwide following a rigorous guidelines development process (1). The committee also overlooked our statement to International Society of Blood Transfusion (ISBT) in December 2022 expressing our concerns about recommending cryoprecipitate (8). The committee appears to have no specialists in hemophilia and allied disorders, yet most treatment in most countries has moved beyond cryoprecipitate for Hemophilia A and fresh frozen plasma for Hemophilia B. The WHO may wish to ensure that its membership reflects the reality of current haemophilia care by including specialists with experience in the new therapies or indeed in the treatment of haemophilia as opposed to solely blood banking or transfusion. Access to appropriate expertise is in everyone's best interest, and there are multiple ways in which to achieve this proactively. We urge the WHO to ensure that any updates to the EML and EMLc do not contradict current disease-specific guidelines.

The WFH is concerned regarding the implied superiority in the cost-effectiveness of PR-Cryo relative to CFCs, through its allocation of core status relative to the complementary status of CFCs. Fully burdened manufacturing costs for recombinant CFCs are frequently lower than plasma derived CFCs, recombinant CFCs are less expensive to purchase than plasma derived clotting factors in some countries and plasma derived CFCs can be purchased in many countries for less than the cost of applying the pathogen reduction process to PR- Cryo. For example, in 2022 a number of countries have reported purchasing plasma derived CFCs for as low as circa € 0.05 per IU (Unpublished data, WFH Annual Global Survey 2022). Indeed, there is a complete absence of information on the actual fully burdened cost of producing PR-cryo (including blood collection). These EML recommendations for non-PR-cryo will directly contribute to morbidity and mortality in coming years should countries follow the WHO EML.

Considering the serious safety concerns outlined above we urge WHO to eliminate non-PR-cryo from the EML immediately. Waiting for the next revision will lead to significant morbidity and mortality in any patient populations exposed to this material. Further we request the EML committee to engage the global hemophilia treaters community, to follow WFH and other regional or national guidelines for the treatment of hemophilia, and to recognize the technology is moving very fast, purchasing costs for CFCs and other

newer treatment products are decreasing, manufacturing costs of recombinant drugs are decreasing, and patients worldwide, including in LIC/LMIC are benefiting from these changes. We urge the WHO to recognize these dynamic changes and reiterate our readiness to offer expertise to inform decisions regarding state-of-the-art hemophilia treatment, which increasingly, LIC/LMIC are accessing or striving to access. All forms of cryo are the past, not the future for persons with hemophilia A worldwide.

Sincerely,

Cesar Garrido
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References:

1. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158. https://onlinelibrary.wiley.com/doi/10.1111/hae.14046
2. Jacobs et al. Survey of blood collection and transfusion practices among institutions in Africa. Transfusion. 2023;1–10. DOI: 10.1111/trf.17501
3. Evatt, Austin, Leon, Ruiz-Sáez, and De Bosch, (2000), Predicting the long-term risk of HIV exposure by cryoprecipitate. Haemophilia, 6: 128-132. https://doi.org/10.1046/j.1365-2516.2000.00057.x
4. Lynch et al. Considerations of pool size in the manufacture of plasma derivatives. TRANSFUSION 1996; 36:770-775.
5. Puerto-Meredith et al. Systematic review of prevalence and risk factors of transfusion transmissible infections among blood donors, and blood safety improvements in Southern Africa. Transfusion Medicine. 2023; 33:355–371. DOI: 10.1111/tme.12988
6. Guidelines on estimation of residual risk of HIV, HBV or HCV infections via cellular blood components and plasma. WHO Technical Report Series, No. 1004, 166-194. 2017.
7. Farrugia, A. The World Health Organisation's list of essential medicines and hae mophilia treatment products. *Haemophilia*. 2023; 1-3. https://doi.org/10.1111/hae.14879
8. WFH Letter to ISBT on the application for inclusion of PR-Cryo in WHO EML and EMLc, December 15, 2022: https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/public-comments/a11_cryoprecipitate-pr_wfh.pdf?sfvrsn=4ffddc96_2

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14 December 2023

Dear Mr Garrido and Dr Pierce,

I refer to your letter of 2 November 2023 regarding the inclusion of pathogen-reduced cryoprecipitate and non-pathogen-reduced cryoprecipitate in the WHO Model Lists of Essential Medicines. In this letter you have raised concerns held by the World Federation of Hemophilia regarding the membership and recommendations of the 2023 Expert Committee on Selection and Use of Essential Medicines and request the removal of non-pathogen-reduced cryoprecipitate from the Model Lists. I am writing to provide clarifications to address and mitigate these concerns.

In making its recommendations, the 2023 Expert Committee considered all information provided, including the application from the International Society of Blood Transfusion, letters of support, public comments (including those from the World Federation of Hemophilia) and expert reviews. To date, only brief details of the Expert Committee's recommendations in the Executive Summary of the meeting report, and the updated Model Lists have been published. These publications alone do not provide the full context of the Committee's considerations and recommendations. Full details will be published in the WHO Technical Report Series (TRS) and excerpts are summarized below, to provide you with more information related to the Committee's recommendations. It is important to highlight that the Committee's recommendation was not limited to the use of pathogen-reduced cryoprecipitate only as a therapeutic alternative to coagulation factor VIII concentrate for the replacement of coagulation factors in haemophilia A, but also included use to replace coagulation factors in cases of massive haemorrhage, von Willebrand disease, and shortage of coagulation factor XIII.

- *The Expert Committee considered that evidence and extensive clinical experience suggest that cryoprecipitate is superior to plasma for replacement of certain clotting factors in a variety of indications in adults and children. However, the Expert Committee noted that concentrated clotting factors remain the preferred treatment for many bleeding disorders and should be prioritized for selection and use wherever possible. The Committee noted and agreed with the WHO Blood Regulatory Network's position statement[1] and reinforced that pathogen-reduced cryoprecipitate ought only to be used in settings where commercial clotting factors are unaffordable or unavailable.*

[1] https://www.who.int/publications/m/item/BRN-Position-Statement-on-Pathogen-reduced-Cryoprecipate

- *The Committee noted that comparative evidence for pathogen-reduced versus non-pathogen-reduced cryoprecipitate is limited but acknowledged that pathogen reduction can eliminate major risks of bloodborne infectious agents and increase the safety of administration. Pathogen-reduced cryoprecipitate has the advantage of an extended shelf life that limits wastage. While there is a risk of alloimmunization and allergic transfusion reaction, these adverse events are lower than rates reported for other blood components, including fresh frozen plasma.*
- *The Expert Committee therefore recommended the inclusion of pathogen-reduced cryoprecipitate on the core list EML and EMLc for use in the replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and shortage of coagulation factor XIII in situations where commercial clotting factors are unaffordable or unavailable. It may also be used as an alternative to coagulation factor VIII concentrate in haemophilia A in settings where this is unavailable or unaffordable.*
- *The Committee also recommended that non-pathogen-reduced cryoprecipitate be included in the Model List as a therapeutic alternative in recognition of the fact that transition to pathogen-reduced cryoprecipitate at the country level may take some time. The Committee acknowledged that solvent and detergent virus inactivation technologies and medical devices used in the plasma fractionation industry are gaining momentum, being adopted by an increasing number of blood establishments and national blood service centers. The Committee considered that every effort should be made to facilitate the transition to pathogen-reduced cryoprecipitate, adopting processing systems based on virus inactivation technologies. For this reason, the Committee considered that removal of non-pathogen-reduced cryoprecipitate from the Model Lists as a therapeutic alternative to pathogen-reduced cryoprecipitate should be considered at earliest opportunity (i.e. 2025) unless an application is received to support its retention. The Committee reiterated that blood donor and donation screening for infections prior to use should be always implemented.*

The Committee's recommendation fully acknowledges the preference for pathogen-reduced over non-pathogen-reduced cryoprecipitate and has foreshadowed the removal of the non-pathogen-reduced form in the future. Under the rules and procedures for WHO Expert Committees, there is no provision for making changes to the Model Lists outside of the Expert Committee process. Therefore, the Federation's request for non-pathogen-reduced cryoprecipitate to be removed from the Model Lists cannot be considered at this time. However, the EML Secretariat will ensure that the recommendation to remove non-pathogen reduced cryoprecipitate is actioned in 2025, unless an application advocating otherwise is received. This approach has been effectively employed by the Expert Committee in the past, where it has been deemed important to allow countries time to transition to adoption of preferred, newly-listed formulations of essential medicines.

Regarding the Federation's concerns around core versus complementary listing, the recommendation to include cryoprecipitate on the core list was made in alignment with the core listing of other blood and blood components in Section 11.1 of the Model Lists. The use of cryoprecipitate as an alternative to coagulation factor VIII in haemophilia A only when coagulation factor VIII concentrate is unaffordable or unavailable has been made explicit in the Committee's full recommendation. Thus, it should not be interpreted that cryoprecipitate has more favourable cost-effectiveness, or should be prioritized for selection and use at the country level over coagulation factor VIII for the treatment of haemophilia A. However, we acknowledge the potential for core versus complementary listings of blood products to be misinterpreted or to inconsistently reflect the intended status of these products in local blood establishments and national blood service centers. The EML Secretariat will undertake a review to address this issue, in consultation with the Federation and other relevant stakeholders.

Regarding newer therapeutic alternatives to coagulation factor VIII for use in haemophilia A, the proposals made in the application by the Federation for bypassing agents and the bispecific monoclonal antibody emicizumab as therapeutic alternatives to coagulation factor VIII were considered by the Expert Committee. However, a comprehensive review of the available evidence as mandated by the WHO procedure for updating the WHO EML, was not provided in the application, thus a recommendation to list could not be made. Nevertheless, in consideration of these medicines:

- *The Expert Committee considered that bypassing agents were not as such therapeutic alternatives to coagulation factors, but rather were currently used in a subset of patients who develop factor VIII or factor IX alloantibodies.*
- *The Expert Committee also considered that the bispecific monoclonal antibody, emicizumab, was not as such a therapeutic alternative to factor VIII, but rather could be used as a separate treatment strategy for patients with haemophilia A.*
- *The Expert Committee acknowledged the potential role of these therapies in changing the treatment paradigm of patients with haemophilia but also noted that currently they might not be considered cost-effective, nor are they widely available. The Committee considered that applications compliant with EML application requirements for these therapies could be considered for independent inclusion in the Model Lists in the future.*

The consideration of new medicines for inclusion on the Model Lists follows a well-established application process and requires submission and evaluation of evidence for clinical efficacy and safety, public health relevance, and comparative cost/cost-effectiveness. The EML Secretariat remains available to support the Federation in the preparation of applications for these therapies for consideration by the Expert Committee in 2025

Members of the Expert Committee are appointed by the WHO Director General based on their professional expertise and experience, while also ensuring equitable geographical and gender balance to provide representation and experience from all WHO regions and across settings of different income levels. The Committee is multi-disciplinary, with members having expertise in fields including but not limited to medicines evaluation, clinical pharmacology, paediatrics, specialized clinical areas, national pharmaceutical policies, health economics, guideline development and evidence synthesis. Expert Committee members are required to collectively consider applications across a wide range of disease areas, which may often be outside their specific areas of expertise, but by virtue of their high levels of skill and experience, are considered well equipped to evaluate all applications and evidence before them.
I am satisfied that the Expert Committee has executed its responsibility appropriately in making recommendations to WHO in relation to the applications for cryoprecipitate and therapeutic alternatives to coagulation factors on the Model Lists. I would like to reassure the Federation that the EML Secretariat will take the actions described above with respect to the removal of non-pathogen-reduced cryoprecipitate from the Model Lists in 2025, and the review of core and complementary listings of all listed blood products. I would like to thank the Federation for its long-standing and valued collaboration with WHO as a non-state actor in official relations and look forward to continuing to work together with the Federation for the next update of the WHO Model Lists of Essential Medicines.

Yours sincerely

Clive Ondari
Director, Health Products Policy and Standards

Dr Clive Ondari
Director
Health Products Policy and Standards
World Health Organization
Geneva, Switzerland

January 18, 2024

Subject: Inclusion of pathogen-reduced cryoprecipitate (PR-Cryo) and non-pathogen-reduced cryoprecipitate (Non-PR Cryo) in the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) in 2023

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Dear Dr. Ondari,

We thank you for your letter dated December 14, 2023 outlining in detail the EML review Expert Committee's recommendations. The World Federation of Hemophilia team will remain in close consultation with the EML Secretariat in preparation of a full application in accordance with the WHO guidelines for the addition of any new therapies in the 2025 EML and EMLc, as recommended by the Expert Committee.

In relation to the question of non-pathogen reduced cryoprecipitate, while we appreciate your reassurance that the EML Secretariat will take actions with respect to the removal of non-pathogen-reduced cryoprecipitate from the Model List in 2025 and the review of core and complementary listings of all listed blood products in consultation with the WFH, it is too little, too late. Considering the significant risk of transmitting bloodborne viruses that will result in mortality and morbidity to hemophilia A patients, and that PR-Cryo is pathogen-reduced, not eliminated, we urge you to revisit this decision as soon as possible without waiting for the planned review process in 2025. These new guidelines, including relegating factor replacement therapies which are well established to prevent morbidity and mortality, in contrast to cryoprecipitate, on the complementary list, is to the detriment of the global hemophilia community. This is especially true in lower income countries that place undue reliance upon the WHO EML.

It is clear adequate knowledge of treatment standards for hemophilia was not available to your expert panel. We reiterate the WFH's readiness to support this review process through our technical experts, leading clinicians in management of hemophilia and

other bleeding disorders, as well as provision of any necessary documentation or published reports on the topic.

We sincerely hope that through joint effort we can avoid exposing hemophilia patients to these serious health risks in timely manner.

Sincerely,

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Appendix 4: Letter of Support from the European Haemophilia Consortium

EHC
Empowering the bleeding disorders community

European Haemophilia Consortium (EHC)
Rue de la Loi 28
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25 October 2024

World Health Organisation
Geneva, Switzerland

Re: European Haemophilia Consortium's support for the World Federation of Hemophilia Applications for the Update of the WHO Lists of Essential Medicines in 2025

We, the European Haemophilia Consortium (EHC), an international non-profit organisation representing 47 national patients' organisations for people with rare bleeding disorders from 27 Member States of the European Union (EU) and most Member States of the Council of Europe, are writing to express our support for the World Federation of Hemophilia Applications for the Update of the WHO Lists of Essential Medicines in 2025. We firmly believe that given great disparities in patient care and availability of treatments for people with bleeding disorders currently persist across Europe, it is high time for WHO Lists of Essential Medicines to reflect the innovation in the field and feature the most efficacious, safe and cost-effective treatments to ensure the survival and well-being of people with haemophilia.

Firstly, acknowledging rapidly evolving treatment landscape for haemophilia and in line with European principles of haemophilia care, we agree with World Federation of Haemophilia's proposal to remove cryoprecipitate from the WHO Lists of Essential Medicines in favour of plasma-derived or recombinant factor VIII and factor IX concentrates - treatments with well-established evidence demonstrating their superior safety and efficacy. Furthermore, while it is possible to virally inactivate cryoprecipitate, it is not common practice and therefore cryoprecipitate should only be used when factor concentrate is not available, making it only suitable for a few deficiencies.

Secondly, we believe that recombinant factors VIII and IX therapeutics for haemophilia must be included in the WHO Lists of Essential Medicines. Recombinant factors VIII and IX are recognised as the main treatment options for both on-demand and primary prophylaxis in children with severe haemophilia. Given their well-established efficacy, recombinant factors VIII and IX are also recommended for secondary prophylaxis in adults as they prevent bleeding episodes, reduce the impact of arthropathy and ultimately improve wellbeing of people with bleeding disorders. Furthermore, while the safety of plasma-derived concentrates has dramatically increased over the years, these concentrates may still pose a risk of infection through emerging pathogens or variant Creutzfeldt-Jakob Disease, thus making recombinant factors VIII and IX a preferred treatment option.

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EHC
Empowering the bleeding disorders community

European Haemophilia Consortium (EHC)
Rue de la Loi 28
1040 Brussels, Belgium

Thirdly, we recommend the inclusion of emicizumab as an individual medicine in the core list of the Essential Medicines List and the Essential Medicines List for Children for the treatment of people with haemophilia A and inhibitors ad well as patients with moderate or severe haemophilia A without inhibitors. In line with European principles of inhibitor management in patients with haemophilia, prophylaxis with emicizumab is now regarded as the optimal therapy in patients with persistent inhibitors, thanks to clinical studies demonstrating superior health outcomes compared to other treatments. It is also proven that emicizumab decrease the number of bleeding episodes and increase quality of life in those with moderate and severe haemophilia A without inhibitors. Further advantages of emicizumab are that it is given by subcutaneous injections at intervals of 1-4 weeks and enables a steady plasma concentration to be maintained (after initial loading doses).

In conclusion, we fully support the World Federation of Haemophilia Applications for the Update of the WHO Lists of Essential Medicines in 2025. We firmly believe that the proposals put forward by the World Federation of Hemophilia will lead to more affordable and equitable haemophilia care and improved health outcomes, survival, and life expectancy among people with haemophilia in Europe. We stand ready to assist in bringing positive change for the bleeding disorders community, as necessary.

Sincerely,

Miguel Crato
President
European Haemophilia Consortium

Olivia Romero Lux
CEO
European Haemophilia Consortium

office@ehc.eu www.ehc.eu

Brussels, 29 October 2024

Subject: IPOPI support letter to WFH's applications for the update of the WHO Lists of Essential Medicines in 2025

To whomever it may concern:

As executive director of the International Patient Organisation for Primary Immunodeficiencies (IPOPI), I am writing to express IPOPI's support to the World Federation of Haemophilia's (WFH) applications to update the WHO Lists of Essential Medicines in 2025:

- Removal of cryoprecipitate (Cryo) which has not been subjected to pathogen reduction processes from the List;
- Inclusion of recombinant coagulation factor VIII and IX therapeutics for haemophilia on the Core List of WHO Model List of Essential Medicines and the List of Essential Medicines for Children;
- Addition of Emicizumab to the WHO Core List Of Essential Medicines And Essential Medicines List For Children for the Treatment of a) people with all severities of haemophilia A and inhibitors to Factor VIII and b) people with severe haemophilia A without Inhibitors to Factor VIII.

IPOPI regularly collaborates with WFH on issues of mutual interest, including the provision of plasma-derived medicinal products (PDMPs). We fully endorse WFH's submission to update the Essential Medicines List (EML), ensuring that patients with haemophilia and other bleeding disorders can access the safest and most effective essential treatments available worldwide.

It is imperative that we move away from outdated and less advanced therapies, such as non-pathogen cryopreserved products, especially when safer and more effective alternatives are readily available. By prioritizing advancements in treatment options and advocating for the inclusion of these safer products on the EML, we can collectively enhance patient safety and improve health outcomes for individuals living with bleeding disorders. It is our responsibility to ensure that all patients receive the highest standard of care, no matter where they live or how rare their disease is.

Sincerely,

Johan Prevot
Executive Director, IPOPI

RARE
DISEASES
INTERNATIONAL

October 30, 2024
Geneva,

Expert Committee on the Selection and Use of Essential Medicines

World Health Organization
20 Avenue Appia
1211 Geneva, Switzerland

Dear Members of the Expert Committee,

On behalf of Rare Diseases International (RDI), I am writing to express our strong support for the World Federation of Hemophilia's (WFH) applications to update the WHO Model Lists of Essential Medicines (EML) in 2025. As a global alliance advocating for equitable access to healthcare for persons living with a rare disease, RDI recognizes the critical role the EML plays in guiding national governments in the selection and financing of essential medicines.

WFH's proposed revisions to the EML for hemophilia and von Willebrand disease (VWD) treatments are both timely and necessary. We fully endorse WFH's recommendation to include prophylactic therapies, which are now recognized as the standard of care for managing hemophilia and are crucial for preventing bleeding episodes and enhancing long-term health outcomes. Ensuring that the EML reflects current clinical practices and includes safe, effective prophylactic treatments will significantly benefit people with hemophilia and VWD globally.

Access to these therapies is particularly vital for individuals affected by rare diseases, many of whom face barriers to essential treatments. By aligning the EML with the latest therapeutic standards, the WHO can help promote health equity and improve the lives of those impacted by these conditions.

RDI fully supports WFH's applications and believes these revisions to the EML will have a meaningful impact on healthcare access and quality of life for people with hemophilia, VWD, and other rare diseases worldwide.

Please do not hesitate to reach out if RDI can provide any additional information to support this important initiative.

Sincerely,

Alexandra Heumber Perry
Chief Executive Officer
Rare Diseases International

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November 1, 2024

World Health Organization (WHO)
Expert Committee on the Selection and Use of Essential Medicines
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Members of the WHO Expert Committee,

On behalf of the International Society on Thrombosis and Haemostasis (ISTH) and the ISTH Global Public Affairs Committee, we are writing to express our strong support for the World Federation of Hemophilia's (WFH) proposal to add emicizumab to the WHO Core List of Essential Medicines and Essential Medicines List for Children. This addition would address critical needs for the treatment of a) people with all severities of hemophilia A who develop inhibitors to Factor VIII and b) people with severe hemophilia A without inhibitors to Factor VIII.

Hemophilia A impacts an estimated 830,895 people globally, including approximately 282,266 with severe disease. The ISTH recognizes the historical under-treatment and high mortality in low-income countries among those living with hemophilia, particularly individuals with severe disease and those who have developed inhibitors to traditional Factor VIII (FVIII) therapy. Emicizumab's unique efficacy as a prophylactic, subcutaneously administered therapy, regardless of inhibitor status, represents a significant advancement in addressing these urgent needs.

The technological advancements over the past six decades in hemophilia treatment underscore a consistent shift towards safer, more effective, and more accessible therapies. Emicizumab, a recombinant bispecific antibody mimicking FVIII function, exemplifies these breakthroughs. Not only does it provide dramatically improved bleeding prevention compared to bypassing agents for individuals with FVIII inhibitors, but it also reduces the annual bleeding rate in people with severe hemophilia A who lack inhibitors. Importantly, emicizumab's demonstrated cost-effectiveness, with evidence indicating it to be less costly than immune tolerance induction or bypassing agents in many countries, adds to its overall public health value.

The ISTH also advocates for the availability of both plasma-derived and recombinant clotting factor concentrates, with a preference for recombinant products, particularly in previously treated patients (PTPs). Furthermore, including FVIII mimicking agents like emicizumab would reduce reliance on single-company solutions, promoting more equitable access to essential therapies.

While technological strides have allowed for recombinant CFCs at reduced costs, the recent WHO listing of pathogen-reduced cryoprecipitate on the Core Essential Medicines List contradicts the principle of non-maleficence given the risks of pathogen transmission. Cryoprecipitate, while able to treat bleeds, does not meet the standard of prophylaxis care essential to preventing bleeds in people with hemophilia. The inclusion of emicizumab as a core medicine would address these critical gaps and support WHO's goal to list the most efficacious, safe, and cost-effective therapies for priority conditions.

The ISTH believes that adding emicizumab to the WHO Core List of Essential Medicines and Essential Medicines List for Children would support the broader availability of a life-saving and life-enhancing treatment, particularly for patients in low- and middle-income countries, thus advancing equitable care and reducing morbidity and mortality worldwide.

Thank you for considering this essential proposal. We are hopeful that the Committee will endorse the inclusion of emicizumab, paving the way for a more accessible, safer, and more effective treatment landscape for those with hemophilia A.

Sincerely,

Flora Peyvandi, M.D., Ph.D.
Donna DiMichele, M.D.
Chairs, ISTH Global Public Affairs Committee
International Society on Thrombosis and Haemostasis (ISTH)