HEMLIBRA®
Injektionslösung zur subkutanen Anwendung
150mg/1,0ml, 105mg/0,7ml, 60mg/0,4ml, 30mg/1,0ml, 300mg/2ml, 12 mg/0.4ml
Zul.-Nr. 66694

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Roche Pharma (Schweiz) AG
Grenzacherstrasse 124
CH-4058 Basel
pharma.schweiz@roche.com
www.roche.ch/pharma
Tel. +41 61 715 41 11

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Hemllibra” is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Hemllibra” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Roche Pharma (Schweiz) AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Hemllibra”.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR HEMLIBRA (EMICIZUMAB)

This is a summary of the risk management plan (RMP) for Hemlibra. The RMP details important risks of Hemlibra, how these risks can be minimized, and how more information will be obtained about Hemlibra's risks and uncertainties (missing information).

Hemlibra's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Hemlibra should be used.

This summary of the RMP for Hemlibra should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Hemlibra's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Hemlibra is authorized for use in adults and children with hemophilia A, with and without factor VIII inhibitors (see SmPC for the full indication). It contains emicizumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Hemlibra's benefits can be found in Hemlibra's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Hemlibra, together with measures to minimize such risks and the proposed studies for learning more about Hemlibra's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures. In the case of Hemlibra these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

- Guide for Healthcare Professionals
- Patient Card
- Patient/Carer Guide
- Guide for Laboratory Professionals

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Hemlibra is not yet available; it is listed under 'missing Information' below.

II.A List of Important Risks and Missing Information

Important risks of Hemlibra are risks that need special risk-management activities to further investigate or minimize the risk, so that the medical product can be safely administered. Important risks can be regarded as either identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hemlibra. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Thromboembolic events (associated with emicizumab and aPCC • Thrombotic microangiopathy (associated with emicizumab and aPCC •
Important potential risks	• Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab • Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions • Thromboembolic events not associated with concomitant use of aPCC
Missing information	• Use in neonates and infants

II.B Summary of Important Risks

Important Identified Risks:

Thromboembolic Events (Associated With Emicizumab and APCC):

Evidence for linking the risk to the medicine	Evidence is based on t*he Phase III studies (BH29884, BH29992, BH30071, and BO39182; N=399),* BO41423 (N=72) *and the Phase I/II study (ACE002JP; N=18) of* emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors. In Studies BH29884, BH29992, BH30071, and BO39182, out of 399 patients receiving emicizumab, 0.5% (2/399) had at least one thromboembolic event associated with the concomitant use of emicizumab and aPCC. There were no thromboembolic events associated with aPCC reported from Study BO41423 as of CCOD (30 Oct 2021). Overall, 6.45% of patients (2/32) who received aPCC while on emicizumab prophylaxis across the Phase III studies had at least one event for this important identified risk of thromboembolic event (associated with emicizumab and aPCC); there were no patients (0/5; 0%) with such an event in Study ACE002JP.
Risk factors and risk groups	There were two patients who experienced thromboembolic events in clinical trials while receiving emicizumab prophylaxis. Both patients received multiple doses of aPCC for the treatment of breakthrough bleeds just prior to developing symptoms. From additional analyses including data on thromboembolic and TMA events, the Sponsor concludes that there is sufficient evidence to support a DDI between aPCC and emicizumab. This interaction is primarily based on the dose and time interval over which aPCC is administered, with average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more associated with an increased risk for developing thromboembolic and TMA events.

Risk minimization measures	Routine risk minimization measures:
	• Provide text In the SmPC regarding this risk
	  ○ Section 4.4: Special warnings and precautions for use
	  ○ Section 4.5: Interaction with other medicinal products and other forms of interaction section
	  ○ Section 4.8: Undesirable effects
	• Provide text in the Package Leaflet regarding this risk Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects
	• Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders
	Additional risk minimization measures:
	• Guide for Healthcare Professionals
	• Patient Card
	• Patient/Carer Guide

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry See Section II.C of this summary for an overview of the post-authorization development plan.

aPCC = activated prothrombin complex concentrate; DDI = drug-drug interaction; EUHASS = European Haemophilia Safety Surveillance; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy

Thrombotic Microangiopathy (Associated With Emicizumab and APCC)

Evidence for linking the risk to the medicine	Evidence is based on the Phase III studies (BH29884, BH29992, BH30071, and BO39182; N = 399), BO41423 (N=72) and the Phase I/II study (ACE002JP; N = 18) of emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors. Of the 399 patients exposed to emicizumab in the Phase III studies BH29884, BH29992, BH30071, and BO39182, 0.75% (3/399) experienced a TMA event associated with the concomitant use of emicizumab and aPCC. There were no TMA events reported from Study BO41423* (N=72) as of the study CCOD (30 Oct 2021). Overall, 9.4% of patients (3/32) who received aPCC while on emicizumab prophylaxis across the Phase III studies experienced this important identified risk of TMA (associated with emicizumab and aPCC); there were no patients (0/5; 0%) with such an even in Study ACE002JP.
Risk factors and risk groups	No specific risk factors for TMA in hemophilia A patients were identified in the literature. However, all cases in the emicizumab clinical program occurred in patients who had taken average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more while receiving emicizumab prophylaxis. Negative re-challenge for one patient restarting emicizumab after resolution of TMA without recurrence support the aforementioned observation as a potential etiology. From additional analyses including data on thromboembolic and TMA events, the Sponsor concludes that there is sufficient evidence to support a DDI between aPCC and emicizumab. This interaction is primarily based on the dose and time interval over which aPCC is administered, with average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more associated with an increased risk for developing thromboembolic and TMA events.

Risk minimization measures	Routine risk minimization measures:
	• Provide text In the SmPC regarding this risk
	  ○ Section 4.4: Special warnings and precautions for use
	  ○ Section 4.5: Interaction with other medicinal products and other forms of interaction section
	  ○ Section 4.8: Undesirable effects
	• Provide text in the Package Leaflet regarding this risk: Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects
	• Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders
	Additional risk minimization measures:
	• Guide for Healthcare Professionals
	• Patient Card
	• Patient/Carer Guide

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry See Section II.C of this summary for an overview of the post-authorization development plan.

aPCC = activated prothrombin complex concentrate; DDI = drug-drug interaction; EUHASS = European Haemophilia Safety Surveillance; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy

Loss of Efficacy Due to Anti-emicizumab Antibodies

Evidence for linking the risk to the medicine	Evidence is based on data from eight Phase III studies (BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881, and MO39129) and the Phase I/II study (ACE002JP) of emicizumab in hemophilia A patients, both with and without FVIII inhibitors*. A total of 36 out of 739 patients tested positive for anti-emicizumab antibodies, of which one patient experienced loss of efficacy.
Risk factors and risk groups	There is no single risk factor for the development of ADAs (Shankar et al. 2007).
Risk minimization measures	Routine risk minimization measures: • Provide text In the SmPC regarding this risk ○ 4.4: Special warnings and precautions for use ○ 4.8: Undesirable effects ○ 5.1: Pharmacodynamic properties • Provide text in the Package Leaflet regarding this risk: ○ Section 2 What you need to know before you use Hemlibra ○ Section 4 Possible side effects with Hemlibra **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations to alert prescribers on the use and management of emicizumab in case of loss of efficacy due to suspected anti-emicizumab antibodies are included in SmPC section 4.4.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry. • PASS based on the PedNET registry. See Section II.C of this summary for an overview of the post-authorization development plan.

ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; FVIII = factor VIII; SmPC = Summary of Product Characteristics

* The Immunogenicity Report V4 was used as the source document for this table which includes the Phase III studies BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881 and MO39129, and the Phase I/II study (ACE002JP).

Important Potential Risks:
Life-threatening Bleeding Due to Misinterpretation of the Standard Coagulation Tests, Which Are Unreliable in Patients Treated With Emicizumab

Evidence for linking the risk to the medicine	In vitro: Emicizumab's mechanism of action and resulting interference was clearly demonstrated in the aPTT and in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials: Data from emicizumab clinical trials (Phase III studies BH29884, BH29992, BH30071, and BO39182, BO41423 and the Phase I/II Study ACE002JP) also demonstrated the effects of emicizumab on laboratory assays. However, no instances of under-treatment of bleeding events due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab, were observed.
Risk factors and risk groups	Standard coagulation laboratory tests based on intrinsic clotting (aPTT, one-stage FVIII activity, including functional (clotting-based) assays for FVIII inhibitors (e.g., Bethesda assays)) are not reliable in the emicizumab setting and do not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. There is a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab if a patient is treated by HCPs other than the emicizumab-prescribing HCP in settings such as an emergency room or in an acute care setting.

Risk minimization measures	Routine risk minimization measures:
	• Provide text In the SmPC regarding this risk
	  ○ Section 4.4: Special warnings and precautions for use
	  ○ Section 4.5: Interaction with other medicinal products and other forms of interaction section
	• Provide text in the Package Leaflet regarding this risk: Section 2 What you need to know before you use Hemlibra
	• Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders
	Additional risk minimization measures:
	• Guide for Healthcare Professionals
	• Patient Card
	• Patient/Carer Guide
	• Laboratory Professional Guide

Additional pharmacovigilance activities	None

aPTT = activated partial thromboplastin time; FVIII = factor VIII; HCP = healthcare professional; SmPC = Summary of Product Characteristics

Anaphylaxis, Anaphylactoid and Systemic Hypersensitivity Reactions

Evidence for linking the risk to the medicine	Evidence is based on data from the Phase III studies (BH29884, BH29992, BH30071 BO39182. BO41423, YO39309, MO39129, JO39881) and Phase I/II Study ACE002JP of emicizumab in hemophilia A patients, both with and without FVIII inhibitors*. Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions are typical potential class effects of subcutaneously administered monoclonal antibodies such as emicizumab. In the Phase I/II Study ACE002JP, 4 out of 18 patients tested positive for anti-emicizumab antibodies. A total of 36 patients from the Phase III studies had developed anti-emicizumab antibodies. There were neither anaphylaxis events nor severe hypersensitivity reactions related to development of anti-emicizumab antibodies across studies. Overall, the safety profile of emicizumab was similar between those patients with anti-emicizumab antibodies and those without. Therefore, these were categorized as important potential risks.
Risk factors and risk groups	Patients with previous history of anaphylaxis and atopic individuals are risk groups. Older age is a risk factor for death from drug-induced anaphylaxis; 73% of all such deaths occurred in patients aged 55 to 85 years old (Liew WK et al. 2009). There is no single risk factor for the development of ADAs in the formation of circulating immune complexes resulting in generalized hypersensitivity reactions (Shankar et al. 2014, Steenholdt et al. 2011).
Risk minimization measures	Routine risk minimization measures: • Provide text in the SmPC regarding this risk ○ SmPC section 4.3: Contraindications • Provide text in the Package Leaflet regarding this risk: • Section 2 What you need to know before you use Hemlibra *No additional measures*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry See Section II.C of this summary for an overview of the post-authorization development plan.

EUHASS = European Haemophilia Safety Surveillance; FVIII = factor VIII; SmPC = Summary of Product Characteristics

* The Immunogenicity Report V4 was used as the source document for this table which includes the Phase III studies BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881 and MO39129, and the Phase I/II study (ACE002JP).

Thromboembolic Events Not Associated With Concomitant Use of APCC

Evidence for linking the risk to the medicine	Cumulated experience indicates that there is insufficient evidence for a causal relationship between emicizumab without concomitant use of aPCC and thromboembolic events. • In the context of a cumulative post-marketing and clinical trial estimated exposure of 28,847 patients worldwide*, a cumulative search of the Roche Global Safety database** (excluding events associated with aPCC) yielded 78 cases comprising 90 thromboembolic events. These cases were all reported in patients with predisposing comorbidities and would not be unexpected in the hemophilia A or general populations. • The incidence, proportion, and rate of thromboembolic events in clinical trials with emicizumab remain within the background incidence in the hemophilia A population (e.g., an incidence rate of 0.17 serious events per 100 patient-years and 0.38 all grade events per 100 patient-years in clinical trials with emicizumab vs. 0.51 events per 100 patient-years[1]). The nonclinical data do not exclude the risk of thromboembolic events with emicizumab alone, but suggest that the risk is not higher from emicizumab administration. The effect of emicizumab on thrombus formation was compared with the effect of rFVIIa and FVIII treatment in a model of venous stasis in normo-coagulative cynomolgus monkeys (Study PHM11-0008). Provoked thrombus formation by emicizumab was equal to the thrombus formation induced by either rFVIIa or FVIII. These results suggest that the risk of emicizumab causing thrombosis does not markedly exceed the risk of rFVIIa preparations or FVIII preparations causing thrombosis. In a second study of data from co-administration of emicizumab and bypassing agents (rFVIIa and aPCC) on thrombus formation in a cynomolgus monkey model of FVIII-deficient hemophilia A/venous stasis (Study PHM12-0023), no thrombosis formation was seen with emicizumab monotherapy. The available data from nonclinical data, clinical trials, literature, and real-world data sources do not support establishing a causal relationship. However with an increase in hemostatic potential as achieved with emicizumab, and as coagulation levels approach that of the general population, there is hypothetical plausibility that thrombotic risk might mirror that of the general population more closely (Barg et al. 2019). Additionally, some studies suggest that in the context of an aging hemophilia A population, with increased comorbidities, that there is a risk of cardiovascular disease (and thus thrombotic risk) similar to that of the general population (Wang 2016, Faghmous et al. 2019, Hofstede et al. 2008). Nonetheless, while emicizumab improves hemostasis closer to normal in a hemophilia A patient; hemostasis is not completely restored and remains below that of a healthy individual (e.g. typically restores to a mid-mild hemophilia phenotype).

	Since all thromboembolic events are closely monitored as part of additional pharmacovigilance activities, thromboembolic events not associated with concomitant use of aPCC have been formally reclassified as an important potential risk for completeness. This reclassification of the potential risk since the first RMP does not reflect a worsening of the benefit-risk profile of emicizumab.
Risk factors and risk groups	Unique risk groups or risk factors have not been determined to date. The observed thromboembolic events (arterial, venous, device related) occurred in patients with relevant past medical history (e.g., underlying cardiovascular risk factors) and/or other contributing comorbidities. Without sufficient evidence to establish a causal relationship, the weighting of potential risk factors or group characteristics cannot yet be determined.
Risk minimization measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry • PASS based on multinational registry study BO44691 See Section II.C of this summary for an overview of the post-authorization development plan.

[1.] Sponsor assessment of claims database, methodology as described in Faghmous et al. 2019

*Worldwide cumulative post-marketing and clinical trial estimated exposure as of 15 November 2023 Source: PBRER 1126611 (Data Lock Point 15 November 2023).

**Cumulative search up to 01 August 2023.

aPCC = activated prothrombin complex concentrate

Missing Information:
Use in Neonates and Infants

Risk minimization measures	Routine risk minimization measures: **Use in neonates and infants** • SmPC section 4.2: Posology and method of administration (special populations)
Additional pharmacovigilance activities	**Use in neonates and infants** • PASS based on the PedNET registry

II.C Post-authorization Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Hemlibra.

II.C.2 Other Studies in Post-authorization Development Plan

Study/activity title: Surveillance of emicizumab-treated patients: an analysis of the EUHASS pharmacovigilance registry (PASS; Study GO40162)
Purpose of the study: The Sponsor participates in the European Haemophilia Safety Surveillance (EUHASS) pharmacovigilance program in order to further characterize the safety profile of patients exposed to emicizumab. The primary objective for this study is as follows: • To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products. The secondary objectives for this study are as follows: • To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and in combination with each of the following drugs: aPCC, recombinant factor VII activate (rFVIIa), and FVIII product. • To describe individual cases of TE and TMA identified in EUHASS. • To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab. • To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information.
Study/activity title: Emicizumab use in pediatric patients in the real world: an analysis of the PedNet registry (PASS; Study MO40685)

Purpose of the study:

The Sponsor collaborates with the PedNet registry in order to generate information regarding the safety, efficacy and utilization of emicizumab in the pediatric population in the post-authorization setting. Safety endpoints of interest are thromboembolic events, thrombotic microangiopathy (TMA) and anaphylaxis, but all adverse events reported to the PedNET registry in patients treated with emicizumab are summarized.

Primary study objective is as follows:

1. To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors

   Primary safety endpoints:

   – Frequency and incidence of thromboembolic events, thrombotic microangiopathy (TMA), anaphylaxis.

Secondary study objectives are as follows:

To evaluate frequency and incidence of any adverse events reported to the PedNet Registry inpatients treated with emicizumab, in all patients and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors.

Secondary safety endpoints:

– Any AEs reported to PedNet Registry.

To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors.

Secondary effectiveness endpoints:

- ABR for treated bleeds and percentage of patients with zero treated bleeds.
- ABR for joint bleeds and major bleeds.
- Bleed counts for soft tissue bleedsand minor bleeds.

2.

Study/activity title: Long-term safety study of emicizumab treatment in patients with moderate HA and severe bleeding phenotype (BO44691) (PASS)

Purpose of the study:

The aim of the study is to evaluate the long-term safety profile of emicizumab in patients with moderate congenital HA (1% ≤ FVIII ≤ 5%) without FVIII inhibitors and with severe bleeding phenotype and who are exposed to emicizumab in real-world settings, with a specific focus on TE events.

The primary objective for this study is to determine the incidence of TE events.

The secondary objectives for this study are:

- To determine the incidence of serious adverse events (SAEs).
- To determine the incidence of thrombotic microangiopathy (TMA) events.
- To determine the incidence of serious systemic hypersensitivity reactions, including anaphylaxis.
- To characterize the risk profile in terms of pre-defined risk factors of TE events in the patient population.