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 minimised, 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 European Public Assessment Report (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 characterise the risks

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

Measures to minimise 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 authorised 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 patient (e.g. with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 medicinal product can be safely administered. Important risks can be regarded as 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).

<table>
<thead>
<tr>
<th>List of important risks and missing information</th>
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<tr>
<td>Important identified risks</td>
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<td>Important potential risks</td>
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**II.B Summary of important risks**

**Important Identified Risk: Thromboembolic events (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 = 373) 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.

Overall, 6.45% of patients (2/31) 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 minimisation 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 Alert Card
- Patient/Carer Guide

**Additional pharmacovigilance activities**

Additional pharmacovigilance activities:
- PASS based on the EUHASS registry
- HCP and patient/carer survey
- PASS based on the PedNET registry

See section II.C of this summary for an overview of the post-authorisation development plan.

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

**Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)**

Evidence for linking the risk

Evidence is based on the Phase III studies (BH29884, BH29992, BH30071, and BO39182; N = 373) and the Phase I/II study
to the medicine (ACE002JP; N = 18) of emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors.

Overall, 9.68% of patients (3/31) 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 minimisation 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 Alert Card
- Patient/Carer Guide

Additional pharmacovigilance activities

Additional pharmacovigilance activities:

- PASS based on the EUHASS registry
- HCP and patient/carer survey
- PASS based on the PedNET registry
See section II.C of this summary for an overview of the post-authorisation development plan.

**Important Potential Risk: Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab**

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>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 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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>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.</td>
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</tbody>
</table>
| Risk minimisation 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 Alert Card |
### Important Potential Risk: 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, and BO39182; N = 373) and the Phase I/II study (ACE002JP; N = 18) 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. 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. ADA may be a risk factor, as it could lead to the formation of circulating immune complexes resulting in generalized hypersensitivity reactions (Shankar et al. 2014, Steenholdt et al. 2011).

Worldwide mortality due to drug-induced anaphylaxis was reported to be up to 20% (Pawankar et al. 2011). A study from 2006 to 2015 reported that the average mortality rate due to hypersensitivity reactions was 6.1% in Japan (Kinoshita et al. 2017).

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).

#### Risk minimisation measures
Routine risk minimization measures:
- Provide text in the SmPC regarding this risk
  - 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 risk minimization 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-authorisation development plan.

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

### Important Potential Risk: Immunogenicity

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<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Evidence is based on data from the Phase III studies (BH29884, BH29992, BH30071, and BO39182) and the Phase I/II study (ACE002JP) of emicizumab in hemophilia A patients, both with and without FVIII inhibitors. There were neither anaphylaxis events nor hypersensitivity reactions related to development of ADAs across studies. Immunogenicity is a typical potential class effect of subcutaneously administered monoclonal antibodies, such as emicizumab. Therefore, it was categorized as an important potential risk.</th>
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<tr>
<td>Risk factors and risk groups</td>
<td>There is no single risk factor for the development of ADAs (Shankar et al. 2007). ADA may be a risk factor as it could lead to the formation of circulating immune complexes resulting in generalized hypersensitivity reactions (Shankar et al. 2014, Steenholdt et al. 2011).</td>
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</tbody>
</table>
| Risk minimisation measures | Routine risk minimization measures:  
  - Provide text in the SmPC regarding this risk  
    - Section 5.1: Pharmacodynamic properties |
| | No additional risk minimization measures. |

**ADA** = anti-drug antibody

### Missing Information

| Risk minimisation measures | Routine risk minimization measures:  
**Use in female patients, pregnancy and lactation:**  
- SmPC section 4.6: Fertility, pregnancy and lactation  
- Package Leaflet Section 2 What you need to know before you use Hemlibra  
**Use in neonates and infants**  
- SmPC section 4.2: Posology and method of administration (special populations)  
**Long term use of emicizumab**  
*No routine measures*  
**Peri-operative management of patients on emicizumab**  
- SmPC section 4.2: Posology and method of administration (special populations)  
**The safety of emicizumab in patients receiving ITI**  
- SmPC section 4.5: Interaction with other medicinal products |

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**II.C Post-authorisation development plan**

**II.C.1 Studies which are conditions of the marketing authorisation**

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

**II.C.2 Other studies in post-authorisation development plan**

**Surveillance of emicizumab-treated patients: an analysis of the EUHASS pharmacovigilance registry (PASS)**

Purpose of the study: the Sponsor will participate in the European Haemophilia Safety Surveillance (EUHASS) pharmacovigilance program in order to further characterize the safety profile of patients exposed to emicizumab. Specifically, the objectives will be to estimate the event rates of the following important risks: thromboembolic events, thrombotic microangiopathy, and anaphylaxis.

**Emicizumab survey to prescribers and patients/carers: effectiveness measure to evaluate awareness and compliance to additional risk minimization measures**

Purpose of the study: Additional risk minimization measures (guide for HCPs, patient/carer guide, patient alert card) will be implemented with the goal to intensify communication and medical and patient education around:

- the important identified risks of TMA (associated with emicizumab and aPCC) and thromboembolic events (associated with emicizumab and aPCC)
- the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab

The main goal of the study is evaluate the awareness, knowledge, and compliance of HCPs and patients/carers to the additional risk minimization measures. Specifically, the surveys will evaluate:

- **Awareness**: what is the HCPs and patients/carers’ awareness that the important risks associated with emicizumab use are in the educational materials: important identified risks of TMA and TE associated with emicizumab and aPCC, important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab

- **Knowledge**: what is the HCPs and patients/carers’ understanding of the risks that may occur if aPCC is used concomitantly with emicizumab, and on emicizumab’s interference with certain laboratory coagulation tests

- **Compliance**: do HCPs and patients/carers’ comply with the guidance provided in the HCP and patient/carer guides
Emicizumab use in pediatric patients in the real world: an analysis of the PedNet registry

Purpose of the study: The Sponsor will collaborate 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 will be thromboembolic events, thrombotic microangiopathy (TMA) and anaphylaxis, but all adverse events reported to the PedNET registry in patients treated with emicizumab will be summarized.

Primary study objective is as follows:

- To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age
  - 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 in patients treated with emicizumab, in all patients and in subgroups determined by age
  - Secondary safety endpoints:
    - Any AEs reported to PedNet Registry
- To describe the bleeding profile of patients treated with emicizumab
  - Secondary efficacy endpoints:
    - Annual bleeding rate (ABR) for treated bleeds and percentage of patients with zero treated bleeds
    - ABR for joint bleeds, ABR for soft tissue bleeds, ABR for major bleeds, ABR for minor bleeds
- To describe administration of coagulation factor products (bypassing agents and FVIII products) in patients receiving prophylactic treatment with emicizumab