Healthcare Professional Guide

Hemlibra (emicizumab) **Subcutaneous injection**

M-AI-00000448

Healthcare Professional Guide

For health care providers to ensure safe use of Hemlibra for treatment of Hemophilia A

- Risk minimization materials for Hemlibra are assessed by the local regulatory authority.
- These materials describe recommendations to minimize or prevent important risks of the drug.
- See the Hemlibra CDS for more information on possible side effects of Hemlibra

Select Important Safety Information

Note: In case a bypassing agent is indicated in a patient receiving Hemlibra prophylaxis, see below for dosing guidance on the use of bypassing agents

Thrombotic microangiopathy associated with Hemlibra and aPCC

1. Cases of thrombotic microangiopathy (TMA) were reported from a clinical trial in patients receiving Hemlibra prophylaxis and high cumulative doses of activated prothrombin complex concentrate (aPCC) were administered

2. Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC

Thromboembolism associated with Hemlibra and aPCC

1. Thrombotic events (TE) were reported from a clinical trial in patients receiving Hemlibra prophylaxis when high cumulative doses of aPCC were administered

2. Patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism when administering aPCC

Laboratory coagulation test interference

1. Hemlibra affects assays for activated partial thromboplastin time (aPTT) and all assays based on aPTT, such as one-stage Factor VIII activity

2. Therefore aPTT based coagulation laboratory test results in patients who have been treated with Hemlibra prophylaxis should not be used to monitor Hemlibra activity, determine dosing for factor replacement or anti-coagulation or measure Factor VIII inhibitor titres

Select Important Safety Information

*This educational material is mandatory as a condition of the marketing authorisation of subcutaneous Hemlibra in the treatment of patients **with congenital hemophilia A** in order to further minimise important selected risks.

PLEASE READ THIS INFORMATION CAREFULLY BEFORE PRESCRIBING THE PRODUCT.

Patient Card and Patient/carer Guide

All patients receiving treatment with Hemlibra should be given a Patient Card and a Patient/caregiver Guide by their healthcare professional. This Patient Card is to be carried by the patient at all times. These materials are to educate patients and their caregivers on the important risks, how to mitigate them, and the need to report any signs or symptoms of these potential adverse events to their treating doctor immediately.

Treating doctors should advise their patients to keep the Patient Card with them at all times and show it to any healthcare professional who may treat them. *This includes **any** doctor, pharmacist, **lab personnel**, nurse or dentist they see - not just the specialist who prescribes their Hemlibra.*

To obtain copies of the Patient Card and Patient/carer Guide, please contact Roche Medical Information department **(cac.medical_info@roche.com)**.

What is Hemlibra?

Medicinal Product

- Hemlibra is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.
- Pharmacotherapeutic group: Antihemorrhagics, ATC code: B02BX06

Mode of Action

- Hemlibra bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis.
- Hemlibra has no structural relationship or sequence homology to factor VIII and, as such, does not induce or enhance the development of direct inhibitors to factor VIII.

Pharmacodynamics

- Prophylactic therapy with Hemlibra shortens the aPTT and increases the reported factor VIII activity (using a chromogenic assay with human coagulation factors). These two pharmacodynamic markers do not reflect the true haemostatic effect of Hemlibra in vivo (aPTT is overly shortened and reported factor VIII activity may be overestimated) but provide a relative indication of the pro-coagulant effect of Hemlibra.

Therapeutic indication

- Hemlibra is indicated for congenital hemophilia A.

Method of Administration

- Please refer to section 2.2 of the CDS for additional information and comprehensive instructions.
- Hemlibra is intended for subcutaneous use only.
- Hemlibra should be administered using appropriate aseptic technique.
- Please refer to the CDS for additional information and comprehensive instructions.

Important identified risks associated with Hemlibra use and how to mitigate them:

Thrombotic microangiopathy associated with Hemlibra and aPCC

- Cases of thrombotic microangiopathy (TMA) were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of >100U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more was administered. **"IMPORTANT: see USPi or SmPC or CDS for details"**

- Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC

Thromboembolism associated with Hemlibra and aPCC

- Thrombotic events (TE) were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of >100U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more was administered. **"IMPORTANT: see USPi or SmPC or CDS for details"**

- Patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism when administering aPCC

Guidance on the use of bypassing agents in patients receiving Hemlibra prophylaxis

- Treatment with prophylactic bypassing agents should be discontinued the day before starting Hemlibra therapy.

- Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving Hemlibra prophylaxis.

- Hemlibra increases patients' coagulation potential. The bypassing agent dose required may therefore be lower than that used without Hemlibra prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding, and the patient's clinical condition.

Important identified risks associated with Hemlibra use and how to mitigate them:

- For all coagulation agents (aPCC, rFVIIa, FVIII, etc.), consideration should be given to verifying bleeds prior to repeated dosing.
- Use of aPCC should be avoided unless no other treatment options/ alternatives are available.
  - If aPCC is the only option to treat bleeding for a patient receiving Hemlibra prophylaxis, the initial dose should not exceed 50 U/kg and laboratory monitoring is recommended (including but not restricted to renal monitoring, platelet testing, and evaluation of thrombosis).
  - If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision with consideration made to laboratory monitoring for the diagnosis of TMA or thromboembolism and verification of bleeds prior to repeated dosing.The total aPCC dose should not exceed 100 U/kg in 24-hours of treatment.
  - Treating physicians must carefully weigh the risk of TMA and TE against the risk of bleeding when considering aPCC treatment beyond 100 U/kg in 24-hours.
- The safety and efficacy of Hemlibra has not been formally evaluated in the surgical setting. If patients require bypassing agents in the perioperative setting, it is recommended that the dosing guidance above for aPCC be followed.
- In clinical trials, no cases of TMA or TE were observed with use of activated recombinant human FVII (rFVIIa) alone in patients receiving Hemlibra prophylaxis; however, the lowest dose expected to achieve hemostasis should be prescribed. Due to the long half-life of Hemlibra, bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of Hemlibra prophylaxis.
- Please refer to section 2.4 of the CDS for additional information and comprehensive instructions.

Important identified risks associated with Hemlibra use and how to mitigate them:

Laboratory coagulation test interference

- Hemlibra affects assays for activated partial thromboplastin time (aPTT) and all assays based on aPTT, such as one stage factor VIII activity (see Table 1 below).
- Therefore, aPTT and one-stage FVIII assay test results in patients who have been treated with Hemlibra prophylaxis should not be used to assess Hemlibra activity, determine dosing for factor replacement or anti coagulation, or measure factor VIII inhibitor titers (see below)
- However, single-factor assays utilizing chromogenic or immuno-based methods are not affected by emicizumab and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays.
- Chromogenic factor VIII activity tests may be manufactured with either human or bovine coagulation proteins.
  - Assays containing human coagulation factors are responsive to Hemlibra but may overestimate the clinical hemostatic potential of Hemlibra.
  - Chromogenic factor VIII activity assays containing bovine coagulation factors are insensitive to Hemlibra (no activity measured) and can be used to monitor endogenous or infused factor VIII activity, or to measure anti-FVIII inhibitors.
- Laboratory tests unaffected by Hemlibra are shown in Table 1 below.
- Due to the long half life of Hemlibra, these effects on coagulation assays may persist for up to 6 months after the last dose (see section 3.2 of the CDS).

Important identified risks associated with Hemlibra use and how to mitigate them:

- **Table 1 Coagulation Test Results Affected and Unaffected by Hemlibra**

Results Affected by Hemlibra	Results Unaffected by Hemlibra
• Activated partial thromboplastin time (aPTT)	• Thrombin time (TT)
• Activated clotting time (ACT)	• One-stage, PT based, single factor assays
• One-stage, aPTT based, single factor assays	• Chromogenic based single-factor assays other than FVIII[1]
• aPTT based Activated Protein C Resistance (APC R)	• Immuno-based assays (e.g. ELISA, turbidometric methods)
• Bethesda assays (clotting based) for FVIII inhibitor titers	• Bethesda assays (bovine chromogenic) for FVIII inhibitor titers
	• Genetic tests of coagulation factors (e.g. Factor V Leiden, Prothrombin 20210)

[1]For important considerations regarding FVIII chromogenic activity assays, see section 2.8 of the CDS

Call for reporting

- Consult the CDS before prescribing, preparing or administering Hemlibra.
- For full information on all possible adverse events please see the CDS.
- Adverse reactions should also be reported to Roche Medical Information via the Company contact point, that is provided below
- Healthcare Professionals treating patients at participating centers are encouraged to participate in and report the adverse events observed to the EUHASS pharmacovigilance system.
- Healthcare Professionals are also encouraged to inform the laboratory director which laboratory tests are affected or unaffected by Hemlibra. The Healthcare Professional should be contacted by the laboratory director to discuss any abnormal test results.

Company contact point

If you have any questions or problems:

Call or write an email:

- (506) 2298-1500
- cac.farmacovigilancia@roche.com

Visit

- www.roche-cac.com