HEALTHCARE PROFESSIONAL GUIDE

▼HEMLIBRA (emicizumab)

Subcutaneous injection

Healthcare Professional Guide* for health care providers to ensure safe use of HEMLIBRA for treatment of Hemophilia A

- Risk minimization materials for HEMLIBRA (emicizumab) are assessed by the Saudi Food and Drug Authority
- These materials describe recommendations to minimize or prevent important risks of the drug.
- See the HEMLIBRA SmPC for more information on possible side effects of HEMLIBRA

▼*This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See final page for details on how to report.*

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

Please read this information carefully before prescribing the product.

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

- 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
- 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 high cumulative doses of aPCC were administered
- Patients receiving HEMLIBRA prophylaxis should be monitored for the development of thromboembolism when administering aPCC

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
- 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

PATIENT ALERT CARD AND PATIENT/CARER GUIDE

All patients receiving treatment with HEMLIBRA should be given a Patient Alert Card and a Patient/caregiver Guide by their healthcare professional. This Patient Alert 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 Alert Card with them at all times and show it to any healthcare professional who may treat them. *This includes **any** doctor, pharmacist, nurse or dentist they see - not just the specialist who prescribes their HEMLIBRA.*

To obtain copies of the Patient Alert Card and Patient/carer Guide, please contact Roche Medical Information department at Company contact point below.

WHAT IS HEMLIBRA?

Medicinal Product

- Emicizumab 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

- Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis.
- Emicizumab 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 emicizumab 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 emicizumab.

Therapeutic indication

- HEMLIBRA 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 factor VIII deficiency) with or without factor VIII inhibitors.

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 SmPC 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 SmPC 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.
- 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 emicizumab 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.

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 emicizumab but may overestimate the clinical hemostatic potential of emicizumab.

- Chromogenic factor VIII activity assays containing bovine coagulation factors are insensitive to emicizumab (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).

Table 1 Coagulation Test Results Affected and Unaffected by HEMLIBRA

Results Affected by HEMLIBRA	Results Unaffected by HEMLIBRA
• Activated partial thromboplastin time (aPTT) • Activated clotting time (ACT) • One-stage, aPTT-based, single-factor assays • aPTT-based Activated Protein C Resistance (APC-R) • Bethesda assays (clotting-based) for FVIII inhibitor titers	• Thrombin time (TT) • One-stage, PT-based, single-factor assays • Chromogenic-based single-factor assays other than FVIII[1] • Immuno-based assays (e.g. ELISA, turbidometric methods) • 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

Loss of efficacy due to suspect anti-emicizumab antibodies

- In case of suspicion of anti-emicizumab antibodies based on clinical evaluation (e.g., increased bleeding episodes), complementary laboratory tests, as described below, may be used (in order of decreasing preference) to estimate decrease in emicizumab exposure and inform treatment decision-making.
- Modified one-stage FVIII activity assay with emicizumab calibrators and controls
    - This assay can be used to detect/estimate emicizumab levels.
    - If the patient is adherent to treatment, decreased activity in this assay could be indicative of the development of clinically important anti-emicizumab antibodies.
- Chromogenic FVIII activity assay (with human coagulation factors)
    - This assay can be used to detect/estimate emicizumab levels.

- If the patient is adherent to treatment, declining FVIII-like activity in this assay could be an indirect indication of loss of exposure due to clinically important anti-emicizumab antibodies.

- aPTT
  - If emicizumab exposure is lost nearly completely, aPTT may be prolonged; however, even at very low emicizumab plasma concentrations, aPTT may remain normal.

Call for reporting

- Consult the CDS before prescribing, preparing or administering HEMLIBRA.
- For full information on all possible adverse events please see the CDS.
- This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the National reporting system that is provided below.
- Adverse reactions should also be reported to Roche Medical Information via the Company contact point that is provided below.
- Healthcare Professionals are also encouraged to inform the laboratory director which laboratory tests are affected or unaffected by emicizumab. The Healthcare Professional should be contacted by the laboratory director to discuss any abnormal test results.
- In case of any adverse events – including any possible side effects not listed in the leaflet – or product complaints associated with the use of HEMLIBRA, please talk to the HCP or report the details in accordance with the national requirements via the national spontaneous reporting systems to:

The National Pharmacovigilance Centre

Land Line: 19999.

Fax: +966112057662

Email: npc.drug@sfda.gov.sa

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Direct Tel. +966 12211 4618

Mobile: +966 5678 44 692
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Company contact point

Should you have any questions regarding the use of HEMLIBRA, please feel free to contact us at jeddah.medinfo@roche.com

Roche Products Saudi Arabia

This document has been reviewed and approved by The Saudi Food and Drug Authority (SFDA)