HEMLIBRA® (EMICIZUMAB)

Solution for subcutaneous injection

HEALTHCARE PROFESSIONAL

This is a guide for healthcare providers to ensure the safe use of HEMLIBRA® for treatment of Haemophilia A

- It describes recommendations to minimize or prevent important risks of the drug.
- For more information on possible side effects of HEMLIBRA®, please refer to the package insert.
- If you have any further questions, please contact your local Roche representative.

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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.

This educational material is mandatory as a condition of the marketing authorisation of subcutaneous HEMLIBRA® in the treatment of patients with haemophilia 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 illovo.medinfo@roche.com

WHAT IS HEMLIBRA®?

Medicinal Product

- HEMLIBRA® (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

- 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

Please refer to the HEMLIBRA® package insert for the indications.

ADMINISTRATION OF HEMLIBRA® SOLUTION FOR SUBCUTANEOUS INJECTION

- HEMLIBRA® is intended for subcutaneous use only.
- HEMLIBRA® should be administered using appropriate aseptic technique.
- Please refer to the package insert 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 >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more was administered **IMPORTANT: see package insert 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 >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more was administered. **IMPORTANT: see package insert 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 the first 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 in the first 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®[1], bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of HEMLIBRA® prophylaxis.

- Please refer to the package insert 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 HEMLIBRA® 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 emicizumab.
    - 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 Pharmacokinetic Properties of the package insert).

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, turbidimetric 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 4.5 of the package insert.

IMPORTANT REMINDER

Call for reporting

- Consult the package insert before prescribing, preparing or administering **HEMLIBRA ®**
- For information on possible adverse events please see the package insert.
- Adverse reactions should also be reported to Roche 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 global.irt_sahubtcs@roche.com
- Healthcare professionals are also encouraged to inform the laboratory director which laboratory tests are affected or unaffected by **HEMLIBRA®**. The Health-care Professional should be contacted by the laboratory director to discuss any abnormal test results.

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FURTHER INFORMATION

For more information about HEMLIBRA® you can contact Roche Medical Information:

Roche Medical Information

e-mail: illovo.medinfo@roche.com or

Tel: +27 800 21 21 25

TO REPORT AN ADVERSE EVENT:

Roche Drug Safety

email: global.irt_sahubtcs@roche.com or

Tel: +27 11 504 4746

Reporting methods e.g., "Any suspected adverse reactions associated with the use of the HEMLIBRA® can be reported to MCAZ through the Adverse Drug Reaction (ADR) reporting form which can be obtained from the MCAZ offices at 106 Baines Avenue, Harare OR can be downloaded from the MCAZ website: www.mcaz.co.zw OR you can report using the ADR reporting platform found on the MCAZ website on the following link: https://primaryreporting.who-umc.org/ZW

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HEMLIBRA® STANDARD BSS

S4 Hemlibra® 30 mg/1 mL, 60 mg/0,4 mL, 105 mg/0,7 mL, 150 mg/1 mL
Abbreviated product information: solution for injection. South Africa: 53/30.1/0071/2/3/4; Namibia: NS2 19/30/0033/4/5/6; Zimbabwe PP 2019/10.7/5815/4/3/2; Botswana S2 BOT2103738/7/6/0.
For full prescribing information, refer to the professional information approved by the Medicines Regulatory Authority.

COMPOSITION: Emicizumab, 30 mg/1 mL, 60 mg/0,4 mL, 105 mg/0,7 mL, 150 mg/1 mL per vial.

INDICATIONS: Hemlibra is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.
There are limited data in infants less than 1 year of age.

DOSAGE: The recommended loading dose is 3 mg/kg administered as a subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of either:
- 1,5 mg/kg once weekly, or
- 3 mg/kg every two weeks, or
- 6 mg/kg every four weeks

CONTRAINDICATIONS: Hypersensitivity to emicizumab or to any of the excipients.

WARNINGS AND PRECAUTIONS: ***Thrombotic microangiopathy (TMA) associated with Hemlibra and activated prothrombin complex concentrate (aPCC):*** Cases of TMA were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more were administered. Monitor for the development of TMA when administering aPCC and immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Consider the risks of resuming Hemlibra prophylaxis following complete resolution of TMA on a case-by-case basis. ***Thromboembolism associated with Hemlibra and activated prothrombin complex concentrate:*** Monitor for the development of thromboembolism when administering aPCC. Immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur, and manage as clinically indicated. Consider the risks of resuming Hemlibra prophylaxis following complete resolution of thrombotic events on a case-by-case basis. ***Guidance on the use of bypassing agents in patients receiving Hemlibra prophylaxis:*** Treatment with bypassing agents should be discontinued 24 hours before starting Hemlibra therapy. Discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use. Avoid use of aPCC unless no other treatment options/alternatives are available. Weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC beyond 100 U/kg in first 24 hours. ***Immunogenicity:*** The presence of neutralising anti-hemlibra antibodies with decreasing Hemlibra concentration may be associated with loss of efficacy. In case of loss of efficacy, evaluate promptly to assess etiology and a possible change in treatment should be considered**.** ***Laboratory coagulation test interference:*** Hemlibra affects intrinsic pathway clotting-based laboratory tests, including the activated clotting time (ACT), activated partial thromboplastin time (aPTT) and all assays based on aPTT, such as one-stage factor VIII activity. Pregnant women are advised not to use Hemlibra. Women should not breastfeed while using Hemlibra. ***Traceability:*** Record batch number of the product and advise patients/caregivers to do the same to improve traceability.

SIDE EFFECTS: The most serious ADRs were TMA and thrombotic events, including cavernous sinus thrombosis and superficial vein thrombosis contemporaneous with skin necrosis. *General disorders and administration site conditions*: Injection site reactions, pyrexia. *Nervous system disorders*: Headache. *Gastrointestinal disorders*: Diarrhoea. *Musculoskeletal and connective tissue disorders*: Arthralgia, Myalgia. *Blood and Lymphatic system disorders*: Thrombotic microangiopathy. *Infections and Infestations*: Cavernous sinus thrombosis. *Skin and subcutaneous tissue disorders:* Skin necrosis. *Vascular Disorders*: Superficial thrombophlebitis.

PACK SIZE: 1 single-use 3 mL vial.

Full details are available from Roche Products (Pty) Ltd, P O Box 1469, Halfway House, 1685. Tel: 011 504 4746 or Toll-free on Roche Ethical Assistance Line (REAL): 0800 21 21 25. www.roche.co.za

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Based on approved date Professional Information: 20 Dec 2022

Last update to BSS: 20 Jan 2023 – Urgent safety update to CDS 7.0