FOR USE IN MALTA

Hemlibra (emicizumab):

Healthcare Professional Guide*

Important Risk Minimisation Information for Healthcare Professionals

This is additional risk minimisation material and is provided by Roche Products (Ireland) Limited as a condition of the Hemlibra marketing authorisation.

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

This material should be read in conjunction with the Summary of Product Characteristics (SmPC), which is available on www.ema.europa.eu

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This educational material is mandatory as a condition of the marketing authorisation, to ensure the safe and effective use of the product and appropriate management of the important selected risks.

Please review the Summary of Product Characteristics (SmPC) in conjunction with this guide before prescribing the product.

- Risk minimisation materials for Hemlibra (emicizumab) are assessed by The Malta Medicines Authority (MMA), Francesca Schembri, Sir Temi Żammit, San Ġwann 3000, Malta.
- These materials describe recommendations to minimise or prevent important risks of the drug.
- See the Hemlibra SmPC for more information on possible side effects of Hemlibra.

Patient Card and Patient/carer Guide

All patients receiving treatment with Hemlibra should be given a Patient Card and a Patient/Carer 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 carers 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 refer to www.ema.europa.eu and download the required material or alternatively if you would like hard copies, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, by telephone (003531 4690700) or email (ireland.drug_surveillance_centre@roche.com).

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 when 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.

Please read this information carefully before prescribing the product.

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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 of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency):
  - with factor VIII inhibitors.
  - without factor VIII inhibitors who have:
    - Severe disease (FVIII < 1%)
    - Moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.
- Hemlibra can be used in all age groups.

Method of Administration

- Please refer to section 4.2 of the SmPC 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 SmPC 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 Summary of Product Characteristics (SmPC) available at www.ema.europa.eu for details].
- Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC.

Thromboembolism associated with Hemlibra and aPCC

- Serious 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 Summary of Product Characteristics (SmPC) available at www.ema.europa.eu 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 the first 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. Caution should be used when treating patients who are at high risk for TMA (e.g. have a previous medical history or family history of TMA), or those who are receiving concomitant medicinal products known to be a risk factor for the development of TMA (e.g. ciclosporin, quinine, tacrolimus).
- 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 4.4 of the SmPC for additional information and comprehensive instructions.

Laboratory coagulation test interference

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.

- 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 utilising 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 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. A chromogenic Bethesda assay utilising a bovine-based factor VIII chromogenic test that is insensitive to emicizumab may be used.
- 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 5.2 of the SmPC).

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, prothrombin time (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 4.4 of the SmPC.

Reporting of suspected adverse reactions

Reporting of suspected adverse events or reactions

Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:
Post: The Drug Surveillance Centre, Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Ireland.
Telephone: 00 353 (1) 469 0700;
Email: ireland.drug_surveillance_centre@roche.com

Alternatively, suspected adverse reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at: http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:
Post: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta
Email: postlicensing.medicinesauthority@gov.mt

Further Information

For electronic copies of this risk minimisation material, refer to the Malta Medicines Authority website [http://www.medicinesauthority.gov.mt/rmm] and download the required material.
Alternatively if you would like hard copies, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24 by mail, telephone [00 353 (1) 469 0700], or email [ireland.drug_surveillance_centre@roche.com].

For further information about this medicine, please contact Medical Information at Roche Products (Ireland) Limited by telephone [00 353 (1) 469 0700], or email [Ireland.druginfo@roche.com].

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