Healthcare Professional Guide

Hemlibra®▼ (emicizumab)

Subcutaneous injection for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors

▼ This medicinal product is subject to additional monitoring. This educational material is provided by Roche Products Limited and Chugai Pharma UK Ltd and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

Full prescribing information can be found in the Hemlibra Summary of Product Characteristics (SmPC): www.medicines.org.uk

Risk minimisation materials for Hemlibra (emicizumab) are assessed by the Medicines Authority. 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.

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 on average a cumulative amount of >100U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more was 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 on average a cumulative amount of >100U/kg/24 hours of aPCC for 24 hours or more was 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.

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Please read this information carefully before prescribing the product.

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, laboratory personnel, 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, medinfo.uk@roche.com or download via www.medicines.org.uk/emc

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

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 routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

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.

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 aPCC for 24 hours or more was administered. 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 aPCC for 24 hours or more was administered. 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.

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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 haemostasis 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

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 on the next page).

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 anticoagulation, or measure factor VIII inhibitor titers (see next page).

However, single-factor assays utilising 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 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. A chromogenic Bethesda assay utilising a bovine-based factor VIII chromogenic test that is insensitive to Hemlibra 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).

Healthcare Professionals are 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.

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, prothrombin time (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, turbidimetric 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 4.5 of the SmPC

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Call for reporting

Consult the SmPC before prescribing, preparing or administering Hemlibra.

For full information on all possible adverse events please see the Summary of Product Characteristics (SmPC), which are available in all EU/EEA languages on the European Medicines Agency website (www.ema.europa.eu).

▼ 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.

Reporting forms and information can be found at www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

As Hemlibra is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Company contact point

If you have any questions or problems:

medinfo.uk@roche.com

www.roche.co.uk

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