PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr HEMLIBRA®

emicizumab injection

Solution

30 mg/mL, 60 mg/0.4 mL (150 mg/mL), 105 mg/0.7 mL (150 mg/mL), 150 mg/mL

Subcutaneous

Professed

Antihemorrhagic

Hoffmann-La Roche Limited

7070 Mississauga Road

Mississauga, ON L5N 5M8

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	12/2022
7 WARNINGS AND PRECAUTIONS	11/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Hemlibra® (emicizumab injection) is indicated for hemophilia A (congenital factor VIII deficiency) patients with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

1.1 Pediatrics

Pediatrics (< 18 years): Hemlibra pharmacokinetics, safety and efficacy data have been collected in 137 pediatric patients between 1 and 18 years of age. There are no clinical efficacy or safety data of Hemlibra in patients less than 1 year of age. Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Hemlibra in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use (see Recommended Dose and Dose Adjustment [4.2] and Pharmacokinetics, Special Populations and Conditions [10.3]).

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of Hemlibra did not include sufficient numbers of patients aged 65 and over to determine whether there are differences in safety or efficacy compared with younger patients.

2 CONTRAINDICATIONS

Hemlibra is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging [6].

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

The following serious adverse reactions have been reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving Hemlibra prophylaxis.

- **Thrombotic microangiopathy (TMA)**
- **Thromboembolism**

Discontinue aPCC at least 24 hours before starting Hemlibra and avoid use of aPCC during Hemlibra treatment unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving Hemlibra prophylaxis, the initial dose should not exceed 50 U/kg. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of Hemlibra if symptoms occur (see Warnings and Precautions [7]).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be initiated under the supervision of a healthcare professional experienced in the treatment of hemophilia and/or bleeding disorders.
- Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy (see Warnings and Precautions, Hematologic [7]).
- FVIII prophylaxis may be continued for the first 7 days of Hemlibra treatment.

4.2 Recommended Dose and Dosage Adjustment

A loading dose of 3 mg/kg Hemlibra once weekly is recommended for the first 4 weeks as a subcutaneous injection. This is followed by a maintenance dose administered one week after the last loading dose. The maintenance dose should be selected based on physician and patient/caregiver dosing regimen preference to support adherence taking into account the age and weight of the patient as outlined below.

Use in Adolescents and Adults ≥ 40 kilograms (kg)

The recommended maintenance dose for adolescents (12-17 years of age) and adults (≥ 18 years of age) who weigh ≥ 40 kg with or without inhibitors to FVIII is 1.5 mg/kg once weekly, or 3 mg/kg every two weeks, or 6 mg/kg every four weeks, administered as a subcutaneous injection. No dosage adjustments of Hemlibra are recommended.

Use in Pediatrics and Patients < 40 kg

The recommended maintenance dose for pediatric patients (< 12 years of age) of any weight or patients of any age who weigh < 40 kg with or without inhibitors to FVIII is 1.5 mg/kg once weekly or 3 mg/kg every two weeks, administered as a subcutaneous injection. No dose adjustments are recommended in pediatric patients (see Clinical Trials, Study Results [14.1] and Pharmacokinetics, Special Populations and Conditions [10.3]).

Use in Geriatrics

No dose adjustments are recommended in patients ≥ 65 years of age. There are no data in patients over 75 years old (see Pharmacokinetics, Special Populations and Conditions [10.3]).

Renal and hepatic impairment

No dose adjustments are recommended in patients with renal or hepatic impairment. Hemlibra has not been studied in patients with severe renal impairment or severe hepatic impairment (see Pharmacokinetics, Special Populations and Conditions [10.3]).

4.3 Reconstitution

Reconstitution is not required.

4.4 Administration

Hemlibra is for subcutaneous use only. Hemlibra should be administered using appropriate aseptic technique.

The injection should be restricted to the recommended injection sites: the abdomen, the upper outer arms and the thighs (see Pharmacokinetics, Absorption [10.3]). No data are available on injection at other sites of the body.

Administration of Hemlibra subcutaneous injection in the upper outer arm should be performed by a caregiver or healthcare professional.

Alternating the site of injection may help prevent or reduce injection site reactions (see Adverse Reactions, Clinical Trials [8.2]). Hemlibra subcutaneous injection should not be administered into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

During treatment with Hemlibra, other medicinal products for subcutaneous administration should, preferably, be injected at different anatomical sites.

Administration by the patient and/or caregiver

Hemlibra is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self-inject Hemlibra, or the patient's caregiver may administer Hemlibra, if their physician determines that it is appropriate.

The physician and the caregiver should determine the appropriateness of a child self-injecting Hemlibra. However, self-administration is not recommended for children below 7 years of age.

Instructions for administration:

Hemlibra solution is a sterile, preservative-free, and ready to use solution for subcutaneous injection that does not need to be diluted.

Hemlibra solution should be inspected visually to ensure there is no particulate matter or discoloration prior to administration. Hemlibra is a colourless to slightly yellow solution. Hemlibra solution should be discarded if particulate matter is visible or the product is discolored.

Refer to the Hemlibra Patient Medication Information for handling instructions when combining vials in a syringe. Do not combine Hemlibra vials of different concentrations (30 mg/mL and 150 mg/mL) in a single syringe.

Hemlibra solution for injection vials are for single-use only.

A syringe, a transfer needle with filter and an injection needle are needed to withdraw Hemlibra solution from the vial and inject it subcutaneously.

A 1 mL syringe should be used for an injection up to 1 mL of Hemlibra solution. Administer doses of Hemlibra greater than 1 mL and up to 2 mL with a 2 mL to 3 mL syringe.

Recommended criteria for syringes and needles are defined to ensure correct and safe administration of Hemlibra. These criteria are based on handling considerations (e.g., dosing accuracy, subcutaneous injection), Hemlibra characteristics (e.g., viscosity), and compatibility between Hemlibra and device materials.

1 mL syringe
Criteria: Transparent polypropylene or polycarbonate syringe with Luer-Lock™ tip (if not available, a syringe with Luer Slip can be used), graduation 0.01 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic.

2 to 3 mL syringe
Criteria: Transparent polypropylene or polycarbonate syringe with Luer-Lock™ tip (if not available, a syringe with Luer Slip tip can be used), graduation 0.1 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic.

Transfer needle with filter:
Criteria: Stainless steel with Luer-Lock™ connection (if not available, a syringe with a Luer Slip connection can be used), sterile, gauge 18 G, length 1" to 1½'', blunt (single-bevelled) or semi-blunt tip, single-use, latex-free, containing a 5-micron filter and non-pyrogenic.

Injection needle:
Criteria: Stainless steel with Luer-Lock™ connection (in case not locally available, a syringe with Luer Slip connection can be used), sterile, gauge 26 G (acceptable range: 25-27 G), length preferably 3/8'' or maximally ½'', single-use, latex-free and non-pyrogenic, preferably including needle safety feature.
Once transferred from the vial to the syringe, the medicinal product should be used immediately since it does not contain any antimicrobial preservative.

Incompatibilities
No incompatibilities between Hemlibra and the recommended syringes and needles have been observed.

Disposal of syringes/sharps
The following procedures should be strictly adhered to regarding the use and disposal of syringes:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location. Local requirements should be followed for the disposal process of unused/expired medicines.

4.5 Missed Dose

If a patient misses a scheduled subcutaneous injection of Hemlibra, the patient should be instructed to take the missed dose as soon as possible, before the day of the next scheduled dose. The patient should then administer the next dose on the usual scheduled dosing day. The patient should not take two doses on the same day to make up for a missed dose.

5 OVERDOSAGE

There is limited experience with overdose of Hemlibra. Accidental overdose may result in hypercoagulability.

Patients who receive an accidental overdose should immediately contact their physician and be monitored closely.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1

1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution, in vials: 30 mg/mL, 60 mg/0.4 mL (150 mg/mL), 105 mg/0.7 mL (150 mg/mL), 150 mg/mL	L-Arginine, L-Aspartic Acid, L-Histidine, Poloxamer 188, water for injection

7 WARNINGS AND PRECAUTIONS

General
In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Advise patients/caregivers to record the batch number of the product whenever Hemlibra is administered outside of a healthcare setting.

Driving and Operating Machinery
There is no evidence that treatment with Hemlibra results in an increase in adverse reactions that might lead to the impairment of the ability to drive and use machines.

Hematologic

Thrombotic microangiopathy associated with Hemlibra and activated prothrombin complex concentrate
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 were administered (see Adverse Reactions, Thrombotic Microangiopathy [8]). Treatment for the TMA events included supportive care with or without plasmapheresis and hemodialysis. Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity. Evidence of improvement was seen within one week following discontinuation of aPCC. Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC. The healthcare professional should immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms and/or laboratory findings consistent with TMA occur, and

manage as clinically indicated. Healthcare professionals and patients/caregivers should weigh the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of TMA on a case-by-case basis.

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 medications known to be a risk factor for the development of TMA (e.g. cyclosporine, quinine, tacrolimus).

Thromboembolism associated with Hemlibra and activated prothrombin complex concentrate
Thrombotic events were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more were administered (see Adverse Reactions, Thromboembolism [8]). No cases required anticoagulation therapy. Evidence of improvement or resolution was seen after discontinuation of aPCC.
Patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism when administering aPCC. The healthcare professional should 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. Healthcare professionals and patients/caregivers should weigh the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of thrombotic events on a case-by-case basis. In case a bypassing agent is indicated in a patient receiving Hemlibra prophylaxis, see below for dosing recommendations for the use of bypassing agents.

Guidance on the use of bypassing agents
Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy. Healthcare professionals 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 the 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 on the patient's clinical condition. Avoid use of aPCC unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving Hemlibra prophylaxis, the initial dose should not exceed 50 U/kg. 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, and 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 thromboembolism against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24-hours.

In clinical trials, no cases of thrombotic microangiopathy or thrombotic events were observed with use of activated recombinant human FVII (rFVIIa) alone in patients receiving Hemlibra prophylaxis. Nonclinical investigations have shown a procoagulant effect of emicizumab on rFVIIa; therefore, a potential risk of thromboembolism cannot be excluded.

Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of Hemlibra prophylaxis (see Pharmacokinetics, Elimination [10.3]).

Immune

Anti-emicizumab antibodies and neutralizing anti-emicizumab antibodies have been reported in 5.1% and 2.7% of patients treated with HEMLIBRA in clinical trials, respectively (see Clinical Trials, Immunogenicity [14.3]). Most patients found to have anti-emicizumab antibodies did not experience a change in emicizumab plasma concentrations or an increase in bleeding events; however, in uncommon (≥ 1/1,000 to < 1/100) cases, the presence of neutralizing anti-emicizumab antibodies with decreasing emicizumab concentration may be associated with loss of efficacy.

In case of clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events), prompt evaluation by a physician should be sought to assess the etiology and a possible change in treatment should be considered.

Monitoring and Laboratory Tests

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 (see Table 2 below). Therefore, intrinsic pathway clotting-based laboratory test results in patients treated with Hemlibra should not be used to monitor Hemlibra activity, determine dosing for factor replacement or anti-coagulation, or measure factor VIII inhibitor titers. Laboratory tests affected and unaffected by Hemlibra are shown in Table 2 below (see Drug-Laboratory Test Interactions [9.7]).

Table 2 Coagulation Test Results Affected and Unaffected by Hemlibra

Results Affected by Hemlibra	Results Unaffected by Hemlibra
Activated partial thromboplastin time (aPTT)	Bethesda assays (bovine chromogenic) for FVIII inhibitor titers
Bethesda assays (clotting-based) for FVIII inhibitor titers	Thrombin time (TT)
One-stage, aPTT–based, single-factor assays (e.g., FVIII activity)	One-stage, prothrombin time-based, single-factor assays
aPTT-based activated protein C resistance (APC-R)	Chromogenic-based single-factor assays other than FVIII*
Activated clotting time (ACT)	Immuno-based assays (e.g., ELISA, turbidimetric methods)
	Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)

*For important considerations regarding FVIII chromogenic activity assays, see Drug-Laboratory Test Interactions [9.7].

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical studies of Hemlibra use in pregnant women. Animal reproduction studies have not been conducted with Hemlibra as the vast majority of patients treated with Hemlibra are males. It is not known whether Hemlibra can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Hemlibra should be used during pregnancy only if the potential benefit for the mother outweighs the potential risk to the fetus.

Contraception
Women of childbearing potential receiving Hemlibra should use effective contraception during, and for at least 6 months after cessation of Hemlibra treatment (see Pharmacokinetics, Elimination [10.3]).

Labour and delivery
The safe use of Hemlibra during labour and delivery has not been established.

7.1.2 Breast-feeding

It is not known whether emicizumab is excreted in human milk. No studies have been conducted to assess the impact of emicizumab on milk production or its presence in breast milk. Human IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Hemlibra and any potential adverse effects on the breastfed infant from Hemlibra or from the underlying maternal condition.

7.1.3 Pediatrics

The safety and efficacy of Hemlibra have been established in pediatric patients. Use of Hemlibra in pediatric hemophilia A patients <12 years of age (with or without FVIII inhibitors) is supported by two randomized studies (HAVEN 3 and HAVEN 1) and three single-arm studies (HAVEN 6, HAVEN 4 and HAVEN 2).

These five clinical studies included a total of 137 pediatric patients in the following age groups: 61 adolescents (12 years to < 18 years), 71 children (2 years to < 12 years) and 5 infants (1 month to < 2 years) (see Clinical Trials, Study Results [14.1]). Safety and efficacy results were consistent with those observed for adults.

7.1.4 Geriatrics

The safety and efficacy of Hemlibra have not been specifically tested in a geriatric population. Clinical studies of Hemlibra included 15 patients aged 65 and over. Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients <65 years and patients ≥65 years (see Recommended Dose and Dose Adjustment [4.2] and Pharmacokinetics, Special Populations and Conditions [10.3]).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse drug reactions (ADRs) are based on pooled data from five phase III clinical trials (three adult and adolescent studies [HAVEN 1, Study BH29884; HAVEN 3, BH30071; HAVEN 4, BO39182], a pediatric study [HAVEN 2, Study BH29992], and an all-age group study [HAVEN 6, Study BO41423]) in which a total of 444 patients with hemophilia A received at least one dose of Hemlibra as routine prophylaxis. Three hundred and seven (69.1%) patients were adults (of which two were female) (≥ 18 years), 61 (13.7%) were adolescents (≥12 to <18 years), 71 (16.0%) were children (≥ 2 to < 12 years) and 5 (1.1%) were infants (≥1 month to < 2 years). The median duration of exposure for safety analysis across the studies was 32.0 weeks (range: 0.1 to 94.3 weeks).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Three patients (0.7%) in the pooled phase III clinical trials receiving Hemlibra prophylaxis withdrew from treatment due to ADRs, which were thrombotic microangiopathy, skin necrosis contemporaneous with superficial thrombophlebitis and headache.

Adverse drug reactions from clinical trials in patients who received Hemlibra are listed by MedDRA system organ class (Table 3).

Table 3 Adverse Drug Reactions Reported in ≥1% of Patients from Pooled Clinical Trials with Hemlibra

System Organ Class **ADR (preferred term, MedDRA)**	**Number of patients (N=444) n (%)**
General disorders and administration site conditions	
Injection site reactions	86 (19.4%)
Pyrexia	23 (5.2%)
Nervous system disorders	
Headache	62 (14.0%)
Gastrointestinal disorders	
Diarrhea	21 (4.7%)
Musculoskeletal and connective tissue disorders	
Arthralgia	63 (14.2%)
Myalgia	13 (2.9%)

Description of selected adverse drug reactions

The most serious adverse drug reactions reported from the clinical trials with Hemlibra were TMA and thrombotic events, including cavernous sinus thrombosis and superficial vein thrombosis contemporaneous with skin necrosis (see below and Warnings and Precautions [**Error! Reference source not found.**]).

Thrombotic microangiopathy

In the pooled phase III clinical trials, thrombotic microangiopathy (TMA) events were reported in less than 1% of patients (3/444) and in 9.7% of patients (3/31) who received at least one dose of aPCC. All 3 TMAs occurred when on average a cumulative amount of > 100 U/Kg/24 hours of aPCC for 24 hours or more was administered during a treatment event (see Warnings and Precautions, Hematologic, Thrombotic microangiopathy) [**Error! Reference source not found.**]. Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity.

Thrombotic events

In pooled phase III clinical trials, serious thrombotic events were reported in less than 1% of patients (2/444) and in 6.5% of patients (2/31) who received at least one dose of aPCC. Both serious thrombotic events occurred when on average a cumulative amount of > 100 U/Kg/24 hours of aPCC for 24 hours or more was administered during a treatment event (see Warnings and Precautions, Hematologic, Thrombotic Events [**Error! Reference source not found.**]).

Characterization of aPCC treatment in *pivotal clinical trials*

There were 82 instances of aPCC treatment, of which eight instances (10%) consisted of on average a cumulative amount of >100 U/kg/24 hours of aPCC for 24 hours or more; two of the eight were associated with thrombotic events and three of the eight were associated with TMA (**Error! Not a valid bookmark self-reference.**). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment. Of all instances of aPCC treatment, 68% consisted of only one infusion < 100 U/kg.

Table 4 Characterization of aPCC Treatment* in Pooled Clinical Trials

Duration of aPCC treatment	Average cumulative amount of aPCC over 24 hours (U/kg/24 hours)		
	<50	50–100	>100
<24 hours	9	47	13
24-48 hours	0	3	1[a]
>48 hours	1	1	7[b]

* An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break. Includes all instances of aPCC treatment excluding those in the first 7 days and those that occurred 30 days after the discontinuation of Hemlibra.

[a] Thrombotic event (1 case)

[b] Thrombotic event (1 case) and thrombotic microangiopathy (3 cases)

Injection site reactions

Injection site reactions (ISRs) were reported very commonly (19.4%) from clinical trials. All ISRs observed in the Hemlibra clinical trials were reported as being non-serious and mild to moderate in intensity and 94.9% resolved without treatment. The most commonly reported ISR symptoms were injection site erythema (10.6%), injection site pain (4.1%); injection site pruritus (2.9%), and injection site swelling (2.7%).

Immunogenicity
In the pooled phase III clinical trials with Hemlibra, 4.9% of patients (36/739) tested positive for anti-emicizumab antibodies and 2.6% of patients (19/739) developed neutralizing anti-emicizumab antibodies. Four patients (0.5%) with neutralizing anti-emicizumab antibodies had an associated decrease in emicizumab concentration. As a consequence of their decreased emicizumab concentrations, their annualized rate of treated bleeding events and annualized rate of all bleeding events were higher compared to those in anti-emicizumab antibody negative patients. There was no clinically apparent impact of the presence of anti-emicizumab antibodies (including neutralizing antibodies) on safety (see Clinical Trials, Immunogenicity [14.3]).

The data reflect the number of patients whose test results were considered positive for antibodies to emicizumab using an enzyme-linked immunosorbent assay (ELISA) and for neutralizing anti-emicizumab antibodies using a FVIII chromogenic assay. Immunogenicity assay results may be influenced by several factors including assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies to emicizumab with the incidence of antibodies to other products may be misleading.

8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

The safety and efficacy of Hemlibra have been established in pediatric patients. Use of Hemlibra in pediatric patients with hemophilia A with FVIII inhibitors is supported by the randomized HAVEN 1 trial (BH29884) and the single-arm HAVEN 2 trial (BH29992) and HAVEN 6 Trial (BO41423). The pooled pediatric safety data included pediatric patients in the following age groups: 61 adolescents (12 years to less than 18 years), 71 children (2 years up to less than 12 years) and 5 infants (1 year up to less than 2 years). No differences in efficacy were observed between the different age groups (see Clinical Trials, Study Results [14.1]).

In general, the adverse reactions in Hemlibra-treated pediatric patients were similar in type to those seen in adult patients.

8.3 Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Thrombotic microangiopathy (0.8%)

Infections and Infestations: Cavernous sinus thrombosis (0.3%)

Skin and subcutaneous tissue disorders: Skin necrosis (0.3%)

Vascular disorders: Thrombophlebitis superficial (0.3%)

8.4 Post-Market Adverse Reactions

The following adverse drug reactions have been identified from post marking surveillance with HEMLIBRA (see Table 5). Adverse drug reactions from post marking surveillance are listed by MedDRA

system organ class.

Table 5 Adverse Drug Reactions from Post marketing Surveillance

System Organ Class ADR (preferred term, MedDRA)	Frequency
Skin and subcutaneous tissue disorders	
Angioedema[a]	Uncommon
Urticaria[b]	Common
Rash[b]	Common

[a] Frequency estimated at the upper limit of the 95% confidence interval utilizing the clinical trial safety population.
[b] Frequency derived from clinical trial data.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Not applicable.

9.2 Drug Interactions Overview

No adequate or well-controlled drug-drug interaction studies have been conducted with Hemlibra.

9.3 Drug-Behavioural Interactions

Not applicable.

9.4 Drug-Drug Interactions

Clinical experience indicates a likely drug interaction exists with Hemlibra and aPCC (see Warnings and Precautions, Hematologic [7] and Adverse Reactions, Clinical Trials [8]).

There is a possibility for hypercoagulability with rFVIIa or FVIII with Hemlibra based on preclinical experiments.

Hemlibra increases coagulation potential, therefore the coagulation factor dose required to achieve hemostasis may be lower than when used without Hemlibra prophylaxis.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Effect of Hemlibra on coagulation tests

Hemlibra restores the tenase cofactor activity of missing activated factor VIII (FVIIIa). Coagulation laboratory tests based on intrinsic clotting (e.g., aPTT) measure the total clotting time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic pathway-based tests will yield overly shortened clotting times with Hemlibra, which does not require activation by thrombin. The overly shortened intrinsic clotting time will then disturb all single-factor assays based on aPTT, such as the one-stage FVIII activity assay (see Warnings and Precautions, Monitoring and Laboratory Tests [7]). However, single-factor assays utilizing chromogenic or immuno-based methods are unaffected by Hemlibra and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays as described below.

Chromogenic FVIII 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. In contrast, assays containing bovine coagulation factors are insensitive to Hemlibra (no activity measured) and can be used to monitor endogenous or infused FVIII activity, or to measure anti-FVIII inhibitors.

Hemlibra remains active in the presence of inhibitors against FVIII and so will produce a false-negative result in clotting-based Bethesda assays for functional inhibition of FVIII. Instead, a chromogenic Bethesda assay utilizing a bovine-based FVIII chromogenic test that is insensitive to Hemlibra may be used.

Due to the long half-life of Hemlibra, effects on coagulation assays may persist for up to 6 months after the last dose (see Pharmacokinetics, Elimination [10.3]).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Emicizumab bridges activated factor IX and factor X to restore the natural function of activated factor VIII that is missing in hemophilia A patients and needed for effective hemostasis.

Emicizumab has no structural relationship or sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII.

10.2 Pharmacodynamics

Hemophilia A is an X-linked hereditary disorder of blood coagulation due to a deficiency of functional FVIII and results in bleeding into joints, muscles or internal organs, either spontaneously or as result of accidental or surgical trauma. Prophylactic therapy with Hemlibra shortens the aPTT and increases the reported FVIII activity (using a chromogenic assay with human coagulation factors). These two pharmacodynamic markers do not reflect the true hemostatic effect of emicizumab *in vivo* (aPTT is overly shortened and reported FVIII activity may be overestimated) but provide a relative indication of the pro-coagulant effect of emicizumab.

10.3 Pharmacokinetics

The pharmacokinetics of emicizumab were determined via a non-compartmental analysis in healthy subjects and using a population pharmacokinetic analysis on a database composed of 389 patients with hemophilia A.

Absorption: Following subcutaneous administration in hemophilia A patients, the absorption half-life was 1.6 days. Following multiple subcutaneous administrations of 3 mg/kg once weekly for the first 4 weeks in hemophilia A patients, mean trough plasma concentrations of emicizumab achieved 52.6±13.6 µg/mL at Week 5.

The mean (±SD) C_{trough} and C_{max} and ratios of C_{max}/C_{trough} at steady state for the recommended maintenance doses of 1.5 mg/kg once weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks are shown in Table 6.

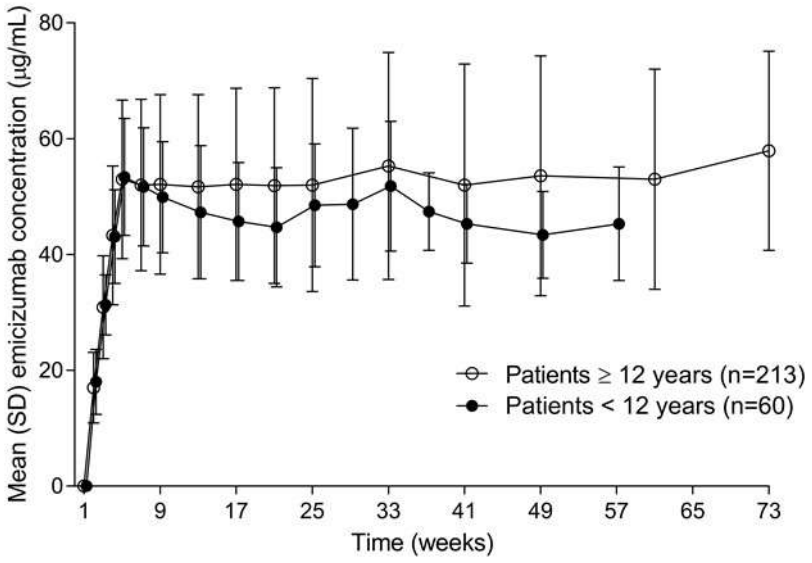
Table 6 Mean (± SD) Steady State Emicizumab Concentrations

	Maintenance Dose		
Parameters	**1.5 mg/kg QW**	**3 mg/kg Q2W**	**6 mg/kg Q4W**
$C_{max, ss}$ (µg/mL)	55.1±15.9	58.3±16.4	67.0±17.7
$C_{avg, ss}$ (µg/mL)	53.7 ±15.6	53.7 ±15.6	53.7 ±15.6
$C_{trough, ss}$ (µg/mL)	51.2±15.2	46.9±14.8	38.5±14.2
$C_{max}/C_{trough\ ratio}$	1.08±0.03	1.26±0.12	1.85±0.47

$C_{avg, ss}$ = average concentration at steady state; $C_{max, ss}$ = maximum plasma concentration at steady state; $C_{trough, ss}$ = trough concentration at steady state; QW = once weekly; Q2W = every two weeks; Q4W = every four weeks. Pharmacokinetic parameters derived from the population PK model.

The PK profiles observed following once weekly dosing (3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week) in adults/adolescents (≥ 12 years) and children (< 12 years) are shown in Figure 1.

Figure 1 **Mean Plasma Emicizumab Concentration versus Time Profiles for Patients ≥ 12 Years (Studies HAVEN 1 and HAVEN 3) Compared with Patients <12 Years (Study HAVEN 2) receiving the 1.5 mg/kg maintenance dose**



In healthy subjects, the absolute bioavailability following subcutaneous administration of 1 mg/kg was between 80.4% and 93.1% depending on the injection site. Similar pharmacokinetic profiles were observed following subcutaneous administration in the abdomen, upper arm, and thigh. Emicizumab can be administered interchangeably at these anatomical sites (see Administration [4.4]).

Distribution: Following a single intravenous dose of 0.25 mg/kg emicizumab in healthy subjects, the volume of distribution at steady state was 106 mL/kg (i.e., 7.4 L for a 70-kg adult). Emicizumab is not intended for intravenous use (see Administration [4.4]). The apparent volume of distribution (V/F), estimated from the population PK analysis, in hemophilia A patients following multiple subcutaneous doses of emicizumab was 10.4 L.

Metabolism: The metabolism of emicizumab has not been studied. IgG antibodies are mainly catabolized by lysosomal proteolysis and then eliminated from or reused by the body.

Elimination: Following single subcutaneous injection in healthy subjects, the elimination half-life was approximately 4 to 5 weeks. Following multiple subcutaneous injections in hemophilia A patients, the apparent clearance was 0.27 L/day and the elimination apparent half-life was 26.9 days.

Special Populations and Conditions

Pediatrics: Lower mean and trough plasma concentrations of emicizumab were observed in pediatric patients compared to adolescents and adults (Figure 1), although no clinically important differences were observed at the recommended loading and maintenance doses (see Recommended Dose and Dosage Adjustment [4.2]).

Geriatrics: Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients < 65 years and patients ≥ 65 years.

Ethnic origin: Population pharmacokinetics analyses in patients with hemophilia A showed that race did not affect the pharmacokinetics of emicizumab.

Gender: There is no sufficient data in female patients to conclude if gender might affect the pharmacokinetics of emicizumab.

Hepatic Insufficiency: Most of the patients with hemophilia A in the population pharmacokinetic analysis had normal hepatic function (bilirubin and AST ≤ ULN, n=300) or mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST, n=51). Only 6 patients had moderate hepatic impairment (1.5 × ULN < bilirubin ≤ 3 × ULN and any AST). Mild or moderate hepatic impairment did not affect the pharmacokinetics of emicizumab (see also Special Dosage Instructions [2.2.1]). Hepatic impairment was defined by the National Cancer Institute (NCI) criteria on hepatic dysfunction.

Renal Insufficiency: No dedicated studies on the effect of renal impairment on the pharmacokinetics of emicizumab have been conducted. Most of the patients with hemophilia A in the population pharmacokinetic analysis had normal renal function (N = 332; creatinine clearance [CLcr] ≥ 90 mL/min) or mild renal impairment (N = 27; CLcr of 60-89 mL/min). Only 2 patients had moderate renal impairment (CLcr of 30-59 mL/min). No patients had severe renal impairment. Mild or moderate renal impairment did not appear to have an impact on the pharmacokinetics of emicizumab (see Recommended Dose and Dose Adjustment [4.2]).

11 STORAGE, STABILITY AND DISPOSAL

Hemlibra should not be used after the expiry date (EXP) shown on the pack.

Store at 2-8ºC. Do not freeze. Do not shake. Keep the vial in the outer carton in order to protect from light. Once removed from the refrigerator, unopened vials can be kept at room temperature (below 30ºC) for up to 7 days. After storage at room temperature, unopened vials may be returned to the refrigerator. Cumulative storage time at room temperature should not exceed 7 days.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: emicizumab

Chemical name: recombinant humanized monoclonal modified IgG4 bispecific antibody that binds to FIX, FIXa, FX, and FXa.

Molecular mass: Approximately 145,637 Da (peptide chains only)

Product Characteristics

Emicizumab is an engineered humanized monoclonal modified immunoglobulin G4 (IgG4) bispecific antibody, bridging factor IXa and factor X. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 7 Summary of patient demographics for clinical trials in hemophilia A patients with or without FVIII inhibitors

Study #	Trial design	Dosage, route of administration and duration	Study patients	Median age (Range) and hemophilia A severity	Sex
HAVEN 1 (BH29884)	Randomized, open-label, Phase 3 study, with two additional nonrandomized arms	Hemlibra SC 3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week	Randomized: Arm A (Hemlibra prophylaxis): N = 35 Arm B (bypassing agent [BPA] on demand): N = 18 Non-Randomized: Arm C (Hemlibra prophylaxis with prior BPA prophylaxis): N = 49	Median: 28 years (12-75) Mild: 3 (3%) Moderate: 3 (3%) Severe: 96 (94%)	Male (100%)
HAVEN 2 (BH29992)	Single-arm, open-label Phase 3 Study	Hemlibra SC 3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week	N = 60	Median: 7.0 years (1-15) Mild: 2 (3%) Moderate: 1 (2%) Severe: 57 (95%)	Male (100%)

Study #	Trial design	Dosage, route of administration and duration	Study patients	Median age (Range) and hemophilia A severity	Sex
HAVEN 3 (BH30071)	Randomized, open-label, Phase 3 study, with an additional nonrandomized arm	Hemlibra SC 3 mg/kg/week for 4 weeks followed by 1.5 mg/kg QW or 3 mg/kg Q2W	Arm A (Hemlibra 1.5 mg/kg QW) N = 36 Arm B (Hemlibra 3 mg/kg Q2W) N = 35 Arm C (Control) N = 18	Median: 38 years (13-77) Severe: 100%	Male (100%)
HAVEN 4 (BO39182)	Single-arm, open-label, Phase 3 study, with a PK run-in part	Hemlibra SC 6 mg/kg Q4W (PK Run-in Part) 3 mg/kg QW for 4 weeks followed by 6 mg/kg Q4W (Expansion part)	N = 48 (41 in expansion part, 7 in PK run-in)	PK Run-in Median: 37 years (14 – 50) Severe: 100% Expansion Part Median: 39 years (14 – 68) Severe: 97.6% Moderate: 0% Mild: 2.4%	Male (100%)
HAVEN 6 (BO41423)	Multicenter, open-label, single-arm study of emicizumab	The emicizumab dosing regimen was loading doses of emicizumab 3 mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W based on patient preference	Enrolled: 72 Treated: 71	Median: 23 years (2-71) Mild: 20 (28.2%) Moderate: 51 (71.8%)	Male: 69 (97.2%) Female: 2 (2.8%)

The efficacy of HEMLIBRA for routine prophylaxis in patients with hemophilia A was evaluated in five clinical studies (three adult and adolescent studies in patients with hemophilia A with or without FVIII inhibitors [HAVEN 1, HAVEN 3, and HAVEN 4], a pediatric study in patients with hemophilia A with FVIII inhibitors [HAVEN 2], and an all-age group study in patients with mild or moderate hemophilia A without FVIII inhibitors [HAVEN 6]).

Clinical studies in adult and adolescent patients with hemophilia A with or without FVIII inhibitors

HAVEN 3 (Study BH30071) – Patients (aged ≥ 12 years old) with hemophilia A without FVIII inhibitors

The HAVEN 3 study was a randomized, multicenter, open-label, phase III clinical study in 152 adolescent and adult males (aged ≥12 years and ≥ 40 kg) with hemophilia A without FVIII inhibitors who previously received either episodic (on demand) or prophylactic treatment with FVIII. Patients received subcutaneous Hemlibra, 3 mg/kg once weekly for the first four weeks followed by either 1.5 mg/kg once weekly (Arms A and D) or 3 mg/kg every two weeks (Arm B) thereafter, or no prophylaxis (Arm C). Patients in Arm C could switch to Hemlibra (3 mg/kg every two weeks) after completing at least 24 weeks without prophylaxis.

Eighty-nine patients previously treated with episodic (on demand) FVIII were randomized in a 2:2:1 ratio to receive Hemlibra either once weekly (Arm A; N = 36), every two weeks (Arm B; N = 35) or no prophylaxis (Arm C; N = 18), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Sixty-three patients previously treated with prophylactic FVIII were enrolled into Arm D to receive Hemlibra (1.5 mg/kg once weekly).

The primary objective of the study was to evaluate in patients previously treated with episodic FVIII the efficacy of prophylactic Hemlibra weekly (Arm A) or every two weeks (Arm B) compared to no prophylaxis (Arm C) based on the number of bleeds requiring treatment with coagulation factors. Other objectives of the study included evaluation of the randomized comparison of Arms A or B and Arm C for the efficacy of Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds.

The efficacy of Hemlibra prophylaxis was also compared with previous prophylactic FVIII treatment (Arm D) in patients who had participated in a non-interventional study (NIS) BH29768 prior to enrollment. Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity as used in HAVEN 3.

The efficacy results of Hemlibra prophylaxis compared with no prophylaxis are shown below in Table 8.

Table 8 Annualized Bleed Rate with Hemlibra Prophylaxis versus No Prophylaxis in Patients ≥ 12 Years of Age without Factor VIII Inhibitors

Endpoint	Arm C: No Prophylaxis (N = 18)	Arm A: Hemlibra 1.5 mg/kg weekly (N = 36)	Arm B: Hemlibra 3 mg/kg every 2 weeks (N = 35)
Treated Bleeds			
ABR (95% CI) [a]	38.2 (22.9; 63.8)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)
% reduction (95% CI), p-value	NA	96% (92.5%; 98.0%), < 0.0001	97% (93.4%; 98.3%), < 0.0001

Endpoint	Arm C: No Prophylaxis (N = 18)	Arm A: Hemlibra 1.5 mg/kg weekly (N = 36)	Arm B: Hemlibra 3 mg/kg every 2 weeks (N = 35)
% patients with 0 bleeds (95% CI)	0.0 (0.0; 18.5)	55.6 (38.1; 72.1)	60.0 (42.1; 76.1)
Median ABR (IQR)	40.4 (25.3; 56.7)	0 (0; 2.5)	0 (0; 1.9)
All Bleeds			
ABR (95% CI) [a]	47.6 (28.5; 79.6)	2.5 (1.6; 3.9)	2.6 (1.6; 4.3)
% reduction (95% CI), p-value	NA	95% (90.1%; 97%), <0.0001	94% (89.7%; 97%), <0.0001
% patients with 0 bleeds (95% CI)	0 (0.0:18.5)	50 (32.9; 67.1)	40 (23.9; 57.9)
Median ABR (IQR)	46.9 (26.1; 73.9)	0.6 (0; 3.9)	1.6 (0; 4.0)
Treated Spontaneous Bleeds			
ABR (95% CI) [a]	15.6 (7.6; 31.9)	1.0 (0.5; 1.9)	0.3 (0.1; 0.8)
% reduction (95% CI), p-value	NA	94% (84.9%; 97.5%), <0.0001	98% (94.4%; 99.4%), <0.0001
% patients with 0 bleeds (95% CI)	22.2 (6.4; 47.6)	66.7 (49.0; 81.4)	88.6 (73.3; 96.8)
Median ABR (IQR)	10.8 (2.1; 26.0)	0 (0; 1.3)	0 (0; 0)
Treated Joint Bleeds			
ABR (95% CI) [a]	26.5 (14.67; 47.79)	1.1 (0.59; 1.89)	0.9 (0.44; 1.67)
% reduction (95% CI), p-value	NA	96% (91.5%; 98.1%), <0.0001	97% (93%; 98.5%), <0.0001
% patients with 0 bleeds (95% CI)	0 (0; 18.5)	58.3 (40.8; 74.5)	74.3 (56.7; 87.5)
Median ABR (IQR)	21.3 (14.5; 41.3)	0 (0; 1.9)	0 (0; 1.3)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile; NA = not applicable
[a] Based on negative binomial regression model.

Patients treated with Hemlibra experienced less treated target joint bleeds, compared to the no prophylaxis arm. The ABR (95% CI) was 0.6 (0.3; 1.4), 0.7 (0.3; 1.6) and 13.0 (5.2; 32.3) for Arm A (Hemlibra 1.5 mg/kg QW), Arm B (Hemlibra 3 mg/kg Q2W) and Arm C (no prophylaxis), respectively. Patients with zero treated target joint bleeds (95% CI) comprised 69.4% (51.9; 83.7), 77.1% (59.9; 89.6) and 27.8% (9.7; 53.5) of the patients in Arm A (Hemlibra 1.5 mg/kg QW), Arm B (Hemlibra 3 mg/kg Q2W) and Arm C (no prophylaxis), respectively.

In the intra-patient analysis, Hemlibra prophylaxis resulted in a statistically significant (p<0.0001) reduction in bleed rate for treated bleeds compared with previous FVIII prophylaxis collected in the NIS prior to enrollment. The mean (NBR model) ABR for patients on Hemlibra and FVIII prophylaxis were 1.5 (95% CI: 1, 2.3) and 4.8 (95% CI: 3.2, 7.1), respectively. The median (IQR) ABR for patients on Hemlibra and FVIII prophylaxis were 0 (95% CI: 0, 2.1) and 1.8 (95% CI: 0, 7.6), respectively. The percentage of patients with zero bleeds on Hemlibra and FVIII prophylaxis were 54.2 (95% CI: 39.2; 68.6) and 39.6 (95% CI: 25.8; 54.7), respectively.

HAVEN 4 (Study BO39182) – Patients (aged ≥ 12 years old) with hemophilia A with or without FVIII inhibitors

Hemlibra was investigated in a single arm, multicenter clinical study in 41 adult and adolescent males (aged ≥ 12 years and ≥ 40 kg) with hemophilia A with or without FVIII inhibitors who previously received either episodic ("on demand") or prophylactic treatment with FVIII or bypassing agents or FVIII. The results for 36 of the 41 patients without inhibitors are reported here (see section 15.2.2 below for the results of the 5 patients with inhibitors to FVIII). Hemlibra prophylaxis consisted of a loading dose of 3 mg/kg Hemlibra once weekly for four weeks followed the next week by a 6 mg/kg Hemlibra maintenance dose that was repeated every four weeks thereafter.

The primary objective of the study was to evaluate the efficacy of Hemlibra prophylaxis in maintaining adequate bleed control, given every four weeks based on treated bleeds. Other objectives were to evaluate the clinical efficacy of Hemlibra prophylaxis on all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds.

Efficacy results for the HAVEN 4 clinical study are summarized below for 36 of the 41 patients ≥12 years old with hemophilia A without inhibitors (see

Table 9). The median observation time of 25.6 weeks (range: 24.1 – 29.4 weeks).

Table 9 Annualized Bleed Rate with Hemlibra Prophylaxis in Patients ≥ 12 Years of Age without Factor VIII Inhibitors

	Hemlibra 6 mg/kg Q4W		
Endpoints	**[a]ABR (95% CI)**	**[b]Median ABR (IQR)**	**% Zero Bleeds (95% CI)**
N =	36	36	36
Treated Bleeds	2.6 (1.5, 4.7)	0 (0; 2.1)	52.8 (35.5, 69.6)
All Bleeds	4.8 (3.2, 7.1)	2.1 (0; 6.1)	27.8 (14.2, 45.2)
Treated Spontaneous Bleeds	0.6 (0.2; 1.6)	0 (0; 0)	83.3 (67.2, 93.6)
Treated Joint Bleeds	1.8 (0.8, 4)	0 (0; 1.9)	69.4 (51.9, 83.7)
Treated Target Joint Bleeds	1.1 (0.4, 3.7)	0 (0; 0)	83.3 (67.2, 93.6)

[a]Calculated with negative binomial regression (NBR) model.
[b]Calculated ABR
Bleed definitions adapted based on ISTH criteria.
Treated bleeds: bleeds treated with FVIII
All bleeds: bleeds treated and not treated with FVIII.
Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks.
ABR= Annualized Bleed Rate; CI= confidence interval; IQR=interquartile range, 25th percentile to 75th percentile; Q4W = once every four week prophylaxis

HAVEN 6 (Study BO41423) – Patients (all ages) with mild or moderate hemophilia A without FVIII inhibitors

The HAVEN 6 study was a multicenter, open-label, single-arm study in 71 emicizumab-treated patients (aged 2 to 71 years, median age 23) with mild (n = 20 [28.2%]) or moderate (n = 51 [71.8%]) hemophilia A without FVIII inhibitors for whom prophylaxis was indicated, as assessed by the investigator. Most patients were male (69 patients [97.2%]), and 2 were female (2.8%). At study entry, 34 patients (47.9%) were on episodic and 37 patients (52.1%) were on prophylactic treatment with FVIII. Patients received subcutaneous HEMLIBRA, 3 mg/kg once weekly for the first four weeks followed by patient preference for one of the following maintenance regimens, from week 5: 1.5 mg/kg once weekly (n = 24 [33.8%]), 3 mg/kg every two weeks (n = 39 [54.9%]) or 6 mg/kg every four weeks (n = 8 [11.3%]), thereafter.

The primary efficacy objective of the study was to evaluate the efficacy of HEMLIBRA prophylaxis based on the number of bleeds requiring treatment with coagulation factors (i.e. treated bleeds) over time. Other objectives were to evaluate the efficacy of HEMLIBRA prophylaxis based on the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds over time

Interim efficacy results for the HAVEN 6 clinical study are summarized in

Table 10. The median observation time is 27.6 weeks (range: 6.7 - 61.7 weeks).

Table 10 HAVENAnnualized Bleed Rate with HEMLIBRA Prophylaxis in Patients with Mild or Moderate Hemophilia A without FVIII Inhibitors

	[c]Hemlibra 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W		
Endpoints	**[a]ABR (95% CI)**	**[b]Median ABR (IQR)**	**% Zero Bleeds (95%CI)**
N	71	71	71
Treated Bleeds	0.8 [0.41;1.46]	0.0 [0.00; 0.00]	80.3 [69.1; 88.8]
All Bleeds	2.3 [1.63; 3.10]	1.5 [0.00; 3.79]	46.5 [34.5; 58.7]
Treated Spontaneous Bleeds	0.1 [0.02;0.23]	0.0 [0.00; 0.00]	95.8 [88.1; 99.1]
Treated Joint Bleeds	0.3 [0.12; 0.65]	0.0 [0.00; 0.00]	90.1 [80.7; 95.9]
Treated Target Joint Bleeds	*Did not converge	0.0 [0.00; 0.00]	94.4 [86.2; 98.4]

[a] Calculated with negative binomial regression (NBR) model

[b] Calculated ABR

Bleed definitions adapted based on ISTH criteria

Treated bleeds: bleeds treated with FVIII.

All bleeds: bleeds treated and not treated with FVIII.

Patients exposed to emicizumab started with a loading dose of 3mg/kg/week for 4 weeks.

ABR=Annualized Bleed Rate, CI=confidence interval; IQR=interquartile range; 25th percentile to 75th percentile; QW=once every week; Q2W=once every two weeks; Q4W=once every four weeks prophylaxis

[c] 1.5 mg/kg QW (n = 24); 3 mg/kg Q2W, (n = 39); 6 mg/kg Q4W (n = 8)

*Model may not converge due to too short follow-up times combined with a low number of bleeds

HAVEN 1 (Study BH29884) – Patients (aged ≥ 12 years old) with hemophilia A with FVIII inhibitors

Hemlibra prophylaxis was evaluated in a randomized, multicenter, open-label clinical study in 109 adolescent and adult males (aged ≥12 years old and ≥40 kg) with hemophilia A with FVIII inhibitors who had previously received either episodic (on-demand) or prophylactic treatment with bypassing agents. In the study, patients received weekly Hemlibra prophylaxis (Arms A and C) 3 mg/kg once weekly for 4 weeks followed by 1.5 mg/kg once weekly thereafter — or no prophylaxis (Arm B).

The majority of patients (60.6%) in the study experienced at least 9 bleeds in the 24 weeks prior to study entry, with 68.6% in Arm A, 72.2% in Arm B and 53.1% in Arm C. Overall, 52.3% of patients in the study were previously treated using Immune Tolerance Induction (ITI), with 40.0% in Arm A, 38.9% in Arm B and 67.3% in Arm C. Target joints involvement was seen in 69.7% of patients in the study, with 71.4% in Arm A, 72.2% in Arm B and 69.4% in Arm C.

Fifty-three patients previously treated with episodic (on-demand) bypassing agents were randomized in a 2:1 ratio to receive Hemlibra prophylaxis (Arm A) or no prophylaxis (Arm B), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Patients randomized to Arm B could switch to Hemlibra prophylaxis after completing at least 24 weeks without prophylaxis.

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled in Arm C to receive Hemlibra prophylaxis. These patients were previously treated with episodic (on-demand) bypassing agents in the non-interventional study (NIS) BH29768.

The primary objective of the study was to evaluate among patients previously treated with episodic (on-demand) bypassing agents the treatment effect of weekly Hemlibra prophylaxis compared with no prophylaxis (Arm A vs. Arm B) on the number of bleeds requiring treatment with coagulation factors over time (minimum of 24 weeks or date of discontinuation). Other secondary objectives of the randomized comparison of Arms A and B were the efficacy of weekly Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds and target joint bleeds, as well as assessing patients' health-related quality of life and health status.

The study also evaluated the efficacy of weekly Hemlibra prophylaxis compared with previous episodic (on demand) and prophylactic bypassing agents (separate comparisons) in patients who had participated in the NIS prior to enrollment (Arms A and C, respectively). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity in both periods.

In HAVEN 1, Hemlibra weekly prophylaxis met all primary and secondary objectives for patients included in the open-label randomized portion of the study (Table 11).

Table 11 Annualized Bleed Rate with Hemlibra Prophylaxis versus No Prophylaxis in Patients ≥ 12 Years of Age with Factor VIII Inhibitors

Endpoint	Arm B: episodic (on-demand) bypassing agents	Arm A: 1.5 mg/kg Hemlibra weekly
	n=18	n=35
Treated Bleeds		
ABR (95% CI)	23.3 (12.3; 43.9)	2.9 (1.7; 5.0)
% reduction (95% CI), p-value	87% (72.3%; 94.3%), <0.0001	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	62.9 (44.9; 78.5)
Median ABR (IQR)	18.8 (13.0; 35.1)	0 (0; 3.7)
All Bleeds		
ABR (95% CI)	28.3 (16.8; 47.8)	5.5 (3.6; 8.6)
% reduction (95% CI), p-value	80% (62.5%; 89.8%), <0.0001	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	37.1 (21.5; 55.1)
Treated Spontaneous Bleeds		
ABR (95% CI)	16.8 (9.9; 28.3)	1.3 (0.7; 2.2)
% reduction (95% CI), p-value	92% (84.6%; 96.3%), <0.0001	
% patients with 0 bleeds (95% CI)	11.1 (1.4; 34.7)	68.6 (50.7; 83.1)
Treated Joint Bleeds		
ABR (95% CI)	6.7 (2.0; 22.4)	0.8 (0.3; 2.2)
% reduction (95% CI), p-value	89% (48%; 97.5%), 0.005	

Endpoint	Arm B: episodic (on-demand) bypassing agents	Arm A: 1.5 mg/kg Hemlibra weekly
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	85.7 (69.7; 95.2)
Treated Target Joint Bleeds		
ABR (95% CI)	3.0 (1.0; 9.1)	0.1 (0.0; 0.6)
% reduction (95% CI), p-value	95% (77.3%; 99.1%), 0.0002	
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	94.3 (80.8; 99.3)

Based on a negative binomial regression (NBR) model and p-value from Stratified Wald test, comparing bleed rate between specified arms.
Arm B: includes no prophylaxis period only.
Bleed definitions adapted based on ISTH criteria.
Treated bleeds: bleeds treated with bypassing agents.
All bleeds: bleeds treated and not treated with bypassing agents.
ABR= Annualized Bleed Rate; CI= confidence interval; IQR=interquartile range, 25th percentile to 75th percentile

In the intra-patient analysis, Hemlibra prophylaxis resulted in a statistically significant reduction in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrollment (Table 12). At the time of the primary analysis, 2 of the 24 patients on Hemlibra prophylaxis had no improvement in their baseline ABR at the data cut-off point.

Table 12 Intra-Patient Comparison of Annualized Bleed Rate (Treated Bleeds) with Hemlibra Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	Arm C_{NIS}: previous treatment with prophylactic bypassing agent	Arm C: Hemlibra 1.5 mg/kg weekly
	N=24	**N=24**
Median Efficacy Period (weeks)	32.1	30.1
Treated Bleeds		
ABR (95% CI)	15.7 (11.1; 22.3)	3.3 (1.3; 8.1)
% reduction (95% CI), p-value	79% (51.4%; 91.1%), 0.0003	
% patients with 0 bleeds (95% CI)	12.5 (2.7; 32.4)	70.8 (48.9; 87.4)
Median ABR (IQR)	12.0 (5.7; 24.2)	0.0 (0.0; 2.2)

Endpoint	Arm C_{NIS}: previous treatment with prophylactic bypassing agent	Arm C: Hemlibra 1.5 mg/kg weekly
Based on a negative binomial regression (NBR) model and p-value from Stratified Wald test, comparing bleed rate between specified arms. Intra-patient comparator data from non-interventional (NIS) study BH29768 Only patients who participated in the NIS BH29768 and in study BH29884 are included. Treated bleeds: bleeds treated with bypassing agents. Bleed definitions adapted based on ISTH criteria. ABR= Annualized Bleed Rate; CI= confidence interval; RR= rate ratio IQR=interquartile range, 25th percentile to 75th percentile.		

Health-related quality of life (HRQoL) for patients aged ≥ 18 years was evaluated at Week 25 for patients enrolled in Arms A and B based on the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire for adults. The Haem-A-QoL is a valid and reliable measure of HRQoL (Table 13).

Table 13 Change in Haem-A-QoL Total Score and Physical Health Score with Hemlibra Prophylaxis versus No Prophylaxis in Patients (>18 Years of Age) with Factor VIII Inhibitors at 25 Weeks

Haem-A-QoL Scores at Week 25	Arm B: episodic (on-demand) bypassing agents (N=16)	Arm A: 1.5 mg/kg Hemlibra weekly (N=31)
Total Score (range 0-100)		
n	14[a]	25[a]
Adjusted mean	43.2	29.2
Difference in adjusted means (95% CI)	14.0 (5.6, 22.5)	
p-value	0.0019	
Physical Health		
N	14	25
Adjusted mean	54.2	32.6
Difference in adjusted means (95% CI)	21.6 (7.9, 35.2)	
p-value	0.0029	

Haem-A-QoL Scores at Week 25	Arm B: episodic (on-demand) bypassing agents (N=16)	Arm A: 1.5 mg/kg Hemlibra weekly (N=31)
Arm B: includes no prophylaxis period only. Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks. Lower scores are reflective of better HRQoL. Clinically meaningful difference: Total score: 7 points; Physical Health: 10 points. [a] Only patients ≥18 years completed the Haem-A-QoL questionnaire.		

HAVEN 2 (Study BH29992) – Pediatric Patients

Hemlibra weekly prophylaxis was evaluated in a single-arm, multicenter, open-label clinical study in pediatric patients (age < 12 years old, or 12 to 17 years old weighing < 40 kg) with hemophilia A with factor VIII inhibitors. Patients received Hemlibra prophylaxis at 3 mg/kg once weekly for the first four weeks followed by 1.5 mg/kg once weekly (QW) thereafter.

The study evaluated the pharmacokinetics, safety, and efficacy of weekly Hemlibra prophylaxis, including the efficacy of weekly Hemlibra prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agent treatment in patients who had participated in the non-interventional study (NIS) BH29768 prior to enrollment (intra-patient comparison).

At the time of the interim analysis, the clinical study had enrolled 60 male patients. Thirty-eight patients aged 6 to < 12 years, 17 patients aged 2 to < 6 years, two patients aged < 2 years and three patients aged ≥ 12 years.

The interim analysis efficacy results for HAVEN 2 are summarized below (see Table 14). Of the 60 patients, 57 patients < 12 years old were evaluable for efficacy; annualized bleed rate and percent of patients with zero bleeds were calculated for 23 patients <12 years of age who received weekly Hemlibra prophylaxis for at least 12 weeks. The median observation time for these patients was 38.1 weeks (range: 12.7 – 41.6).

Table 14 Annualized Bleed Rate with Hemlibra Prophylaxis in Pediatric Patients < 12 Years of Age (Interim Analysis)

	Hemlibra 1.5 mg/kg weekly		
Endpoint	**[a]ABR (95% CI)**	**[d]Median ABR (IQR)**	**% Zero Bleeds (95% CI)**
[b]N	**23**	**23**	**23**
Treated Bleeds	0.2 (0.1; 0.6)	0.0 (0.0; 0.0)	87.0 (66.4; 97.2)
All Bleeds	2.9 (1.8; 4.9)	1.5 (0.00; 4.53)	34.8 (16.4; 57.3)

	Hemlibra 1.5 mg/kg weekly		
Endpoint	**[a]ABR (95% CI)**	**[d]Median ABR (IQR)**	**% Zero Bleeds (95% CI)**
[b]N	**23**	**23**	**23**
Treated Spontaneous Bleeds	0.1 (0.0; 0.5)	0.0 (0.0; 0.0)	95.7 (78.1; 99.9)
Treated Joint Bleeds	0.1 (0.0; 0.5)	0.0 (0.0; 0.0)	95.7 (78.1; 99.9)
Treated Target Joint Bleeds	[c]Not Estimable	0.0 (0.0; 0.0)	100.0 (85.2; 100.0)

[a]Calculated with negative binomial regression (NBR) model.

[b]Efficacy data from treated patients aged < 12 years who had been on study BH29992 for at least 12 weeks (n = 23)

[c]No treated target joint bleeds were reported.

[d]Calculated ABR

Bleed definitions adapted based on ISTH criteria.

Treated bleeds: bleeds treated with bypassing agents.

All bleeds: bleeds treated and not treated with bypassing agents.

Patients exposed to emicizumab started with a loading dose of 3 mg/kg/week for 4 weeks.

ABR= Annualized Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

In the intra-patient interim analysis, weekly Hemlibra prophylaxis resulted in a clinically meaningful (99%) reduction in bleed rate for treated bleeds in 13 pediatric patients after at least

12 weeks of treatment compared to their bleed rate collected in the NIS prior to enrollment (see

Table 15).

Table 15 Intra-Patient Comparison of Annualized Bleed Rate (Treated Bleeds) with Hemlibra Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	Previous treatment with prophylactic bypassing agent	Hemlibra 1.5 mg/kg weekly
	N=13	N=13
Treated Bleeds		
ABR (95% CI)	17.2 (12.4; 23.8)	0.2 (0.1; 0.8)
% reduction (95% CI)	99% 0.01 (0.00; 0.04)	
% patients with 0 bleeds (95% CI)	7.7 (0.2; 36.0)	84.6 (54.6; 98.1)
Median ABR (IQR)	14.3 (11.02;24.35)	0.0 (0.00;0.00)

Confidence interval comes from negative binomial regression (NBR) model

Intra-patient comparator data from non-interventional study (NIS) BH29768

Only patients <12 years old who participated in the NIS BH29768; and in study BH29992 for at least 12 weeks are included.

Treated bleeds: bleeds treated with bypassing agents.

Bleed definitions adapted based on ISTH criteria.

ABR= Annualized Bleed Rate; CI= confidence interval; RR= rate ratio

Note: 12 patients received prior bypassing agent prophylactic; 1 patient received prior episodic bypassing agents.

HAVEN 4 (BO39182) – Adolescents and Adults

Efficacy of the 6 mg/kg every 4-week maintenance Hemlibra prophylactic dosing regimen was evaluated in a subgroup of 5 hemophilia A patients with FVIII inhibitors based on the bleed rate for bleeds requiring treatment with coagulation factors. The median observation time was 26.1 weeks (range 24.4 – 28.6 weeks). Hemlibra prophylaxis resulted in an ABR (95% CI) for treated bleeds of 1.2 (0.1, 14.8) based on negative binomial regression. On Hemlibra prophylaxis with 6 mg/kg every 4 weeks, 4 patients with FVIII inhibitors had zero treated bleeds. Although limited by small patient numbers, the efficacy of the 6 mg/kg every 4-week maintenance dose is consistent with the results observed for this dosing regimen in hemophilia A patients without inhibitors.

14.2 Comparative Bioavailability Studies

Not applicable.

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

A total of 739 patients were tested for anti-emicizumab antibodies in the pooled phase III clinical trials, of which 36 patients (4.9%) tested positive for anti-emicizumab antibodies. In 19 patients (2.6%), anti-emicizumab antibodies were neutralizing *in vitro*. Of these 19 patients, the neutralizing anti-emicizumab antibodies did not appear to have a clinically meaningful impact on the pharmacokinetics or efficacy of HEMLIBRA in 15 patients, while decreased emicizumab plasma concentrations were observed in four patients (0.5%). For these four patients, the median annualized bleed rates for treated and all bleeds were 14.1 (vs. 0.4-1.0 for other anti-emicizumab antibody statuses) and 15.2 (vs. 0.5-2.3 for other anti-emicizumab antibody statuses), respectively.

There was no apparent clinical impact of the presence of anti-emicizumab antibodies on safety. However, this is based on a small number of patients who developed these anti-emicizumab antibodies.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Preclinical data reveal no special hazards for humans based on studies of acute and repeated dose toxicity, including safety pharmacology endpoints and endpoints for reproductive toxicity.

Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of emicizumab.

Genotoxicity
No studies have been performed to establish the mutagenic potential of emicizumab.

Impairment of fertility
Emicizumab did not cause any toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses of up to 30 mg/kg/week in subcutaneous general toxicity studies of up to 26-week duration and at doses of up to 100 mg/kg/week in a 4-week intravenous general toxicity study.

Repeat dose toxicology
The cynomolgus monkey was selected as the species of choice in the nonclinical safety assessment on the basis of its cross-reactivity for emicizumab. Cynomolgus monkeys have been administered emicizumab weekly for 4 weeks in duration by the IV route and for up to 26 weeks in duration by the SC route. Safety pharmacology endpoints (CNS, cardiovascular, respiratory system) and fertility endpoints (testicular size, sperm examinations, menstrual cyclicity) were included in the general toxicity studies. No toxicological changes attributable to SC or IV administration of emicizumab were observed; the NOAEL was the highest tested dose in each study (i.e., 100 mg/kg/week for IV dosing and 30 mg/kg/week for SC dosing).

Reproductive toxicity
No data are available with respect to potential side effects of emicizumab on embryo-fetal development.

Other
In an in vitro study of cytokine release that used the whole blood of healthy adults, the levels of cytokines induced by emicizumab were comparable to those induced by other low-risk antibodies.

Using FVIII-deficient human plasma, emicizumab shortened in vitro the pathologically prolonged aPTT in a concentration-dependent manner and also promotes thrombin generation triggered by activated factor XI (FXIa). As emicizumab has no structural relationship with human FVIII (hFVIII), its procoagulant potency was fully retained in the presence of inhibitors to FVIII. In a cynomolgus monkey hemophilia A model subcutaneous (SC) and intravenous (IV) administration of emicizumab corrected abnormal prolonged aPTT and prevented spontaneous and provoked tissue and joint bleeding. There is a possibility for hypercoagulability with emicizumab in combination with aPCC, rFVIIa or FVIII based on preclinical experiments.

17 SUPPORTING PRODUCT MONOGRAPHS

FEIBA NF (Anti-Inhibitor Coagulant Complex) Product Monograph. Shire Pharma Canada ULC., April 2018.

NiaStase RT® (eptacog alfa [activated]) Product Monograph. Novo Nordisk Canada Inc., November 2017.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

(hem-lee-bruh)

HEMLIBRA®

emicizumab injection

Read this carefully before you start taking **Hemlibra®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Hemlibra**.

Serious Warnings and Precautions

Hemlibra increases the potential for your blood to clot and may cause the following serious side effects when used with another drug to treat bleeding known as aPCC (activated prothrombin complex concentrate):

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to your kidneys, brain, and other organs. Symptoms include confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, stomach or back pain, nausea or vomiting, feeling sick or decreased urination.
- **Blood clots (thromboembolism).** Blood clots may form in blood vessels in your arm, leg, lung, or head. Symptoms include swollen arms or legs, pain or redness in arms or legs, difficulty breathing, chest tightness, fast heart rate, coughing blood, feeling faint, headache, numbness in your face, eye pain or swelling, or trouble seeing.

Stop taking aPCC at least twenty-four hours before starting Hemlibra. Avoid taking aPCC while taking Hemlibra unless no other treatments are available. If aPCC is required, take no more than 50 units per kilogram (U/kg). If you feel that you need more than 100 U/kg to control bleeding talk to your healthcare professional. If you experience symptoms described here, stop taking aPCC and Hemlibra and seek medical help.

Your doctor should monitor you closely for these side effects if it is recommended that Hemlibra and aPCC be taken at the same time.

What is Hemlibra used for?

Hemlibra is a medicine that can be used by all age groups. It is used to treat people:

- who have haemophilia A (a bleeding condition people can be born with or develop), which is caused by a missing or faulty protein (factor VIII) that prevents blood from clotting normally,
- who have also developed “factor VIII inhibitors” that prevent replacement factor VIII

from working properly,
- or by patients who do not have “factor VIII inhibitors”

This medicine is to be used weekly, every 2 weeks or every 4 weeks unless your doctor tells you to stop taking it.

How does Hemlibra work?

Hemlibra contains the active substance “emicizumab”. This belongs to a group of medicines called “monoclonal antibodies”. Monoclonal antibodies are a type of protein that recognises and binds to a target in the body. Factor VIII is a protein that helps the body form clots and stop bleeding by binding to other proteins. When people have haemophilia A, factor VIII is missing or not working properly. Hemlibra works like Factor VIII, by binding to the same clotting factors as Factor VIII, which helps your blood to clot. Hemlibra is injected under the skin (subcutaneously).

What are the ingredients in Hemlibra?

Medicinal ingredients: emicizumab

Non-medicinal ingredients: L-arginine, L-histidine, L-aspartic acid, Poloxamer 188 and water for injection.

Hemlibra comes in the following dosage forms:

Solution, in vials of 30 mg/mL, 60 mg/0.4 mL (150 mg/mL), 105 mg/0.7 mL (150 mg/mL), 150 mg/mL. Reconstitution is not required.

Do not use Hemlibra if:

- you are allergic to emicizumab or any of the other ingredients of this medicine or components of the container

To help avoid side effects and ensure proper use, talk to your health professional before you take Hemlibra. Talk about any health conditions or problems you may have, including if you:

Before you start using Hemlibra, it is very important you talk to your doctor about when and how to use “bypassing agents” while receiving Hemlibra, as this may differ from before. Examples of bypassing agents include “activated prothrombin complex concentrate” (aPCC, also called FEIBA NF) and “recombinant FVIIa” (rFVIIa, also called eptacog alfa or NiaStase RT®).

Serious and potentially life threatening side effects have been observed when aPCC was used in patients who were also receiving Hemlibra. For more information, see below in “The following may interact with Hemlibra, Using a bypassing agent while receiving Hemlibra”.

Be aware of the potentially serious side effects of using aPCC while receiving Hemlibra. In a study, the following serious side effects have been reported when aPCC was used in patients also receiving Hemlibra:

- Thrombotic microangiopathy
    - Thrombotic microangiopathy is a serious and potentially life threatening condition.
    - When people have thrombotic microangiopathy, the lining of the blood vessels can be damaged and blood clots may develop in small blood vessels. In some cases, this can cause damage to the kidneys and/or other organs.
    - It is important to know the symptoms of thrombotic microangiopathy, in case you develop the condition (see below in "What are possible side effects from using Hemlibra?").
    - Stop using Hemlibra and aPCC, and talk to a doctor immediately if you or your caregiver notices any symptoms of thrombotic microangiopathy.

- Blood clots (thromboembolism)
    - Blood clots may form. In rare cases, a blood clot can block blood vessels and may be life threatening.
    - It is important to know the symptoms of blood clots, in case clots develop (see below in "What are possible side effects from using Hemlibra?").
    - Stop using Hemlibra and aPCC, and talk to a doctor immediately if you or your caregiver notices any symptoms of blood clots.

Stop using Hemlibra and aPCC, and talk to doctor immediately if you or your caregiver notices any symptoms of blood clots.

Other warnings you should know about:

Laboratory tests

Tell your doctor if you are using Hemlibra before you have laboratory tests that measure how well your blood is clotting. This is because the presence of Hemlibra in the blood may interfere with some of these laboratory tests, leading to inaccurate results.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. Your doctor will consider the benefit of you taking Hemlibra against the risk to your baby. You should use an effective method of birth control (contraception) during treatment with Hemlibra and for 6 months after your last injection of Hemlibra.

Immunogenicity

Your body may make antibodies against Hemlibra, which may stop Hemlibra from working properly. Contact your healthcare provider immediately if you notice that Hemlibra has stopped working for you (e.g. increase in bleeds).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Hemlibra:

Using a bypassing agent while receiving Hemlibra

- Before you start using Hemlibra, talk to your doctor and carefully follow their instructions regarding when to use a bypassing agent and the dose and schedule you should use. Hemlibra increases the ability of your blood to clot. Therefore, the dose of bypassing agent required may be lower than the dose you used prior to starting Hemlibra.
- Avoid using aPCC unless no other treatment options are available. However, if aPCC is required, talk to your doctor in case you feel you need more than 50 units/kg of aPCC total.

Educational materials for Healthcare Professionals and patients are available from Hoffmann-La Roche Limited by calling 1-888-762-4388.

How to take Hemlibra:

A doctor qualified to care for patients with hemophilia will start you on treatment with Hemlibra. Always use this medicine exactly as your doctor has told you. Check with your healthcare provider if you are not sure.

Keeping a record

Each time you use Hemlibra, record the name and batch number of the medicine.

How Hemlibra is given

If you or your caregiver gives an injection of Hemlibra, please refer to the Instruction for Use at the end of this leaflet.

- Hemlibra is given by injection under the skin (subcutaneously).
- Your doctor or nurse will show you and/or your caregiver how to inject Hemlibra.
- Once you and/or your caregiver have been trained, you should be able to inject this medicine at home, by yourself or with the help of a caregiver.
- Do not inject Hemlibra into a vein or muscle. To correctly insert the needle under the skin, pinch a fold of loose skin at the clean injection site with your free hand. Pinching the skin is important to ensure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injecting into a muscle could result in an uncomfortable injection.
- Prepare and give the injection under clean and germ-free conditions using “aseptic technique”. You will be given more information about this by your doctor or nurse.
- Before using the medicine, check the solution for particles or discolouration. The solution should be clear to slightly yellow. Do not use this medicine if you notice that it is cloudy, discoloured, or contains visible particles.

Where to inject Hemlibra

- Your doctor will show you and/or your caregiver which areas of the body should be injected with Hemlibra.
- The recommended places to give an injection are: the front of the waist (lower abdomen), upper outer arms, or the front of the thighs. Only give an injection in the recommended places.

- Each time you or your caregiver gives an injection, use a different area of the body to the one you used before, using one of the recommended places (front of the waist, upper outer arms, or the front of the thighs).
- Do not give injections where the skin is red, bruised, tender, hard, or areas where there are moles or scars.
- When using Hemlibra, other medicines injected under the skin should be given in a different area.

Using syringes and needles

- A syringe, a transfer needle with filter and an injection needle are needed to withdraw the Hemlibra solution from the vial into the syringe and inject it under the skin.
- Syringes, transfer needles with filter and injection needles are not provided in this pack. For more information, see the "Instructions for Use" below.
- Make sure that you use a new injection needle for each injection and dispose of it after a single use.
- A 1 millilitre syringe should be used for an injection up to 1 millilitre of Hemlibra solution.
- A 2 to 3 millilitre syringe should be used for an injection greater than 1 millilitre and up to 2 mL of Hemlibra solution.

Use in children and adolescents

Hemlibra can be used in children and adolescents of all ages (for the recommended dose, see "Usual dose").

- If a child would like to self-inject the medicine, the child's healthcare provider and the parent or caregiver should agree on whether it is appropriate for them to do so. Self-injection for children below the age of 7 years is not recommended.

Usual dose:

- Weeks 1 to 4: The dose is 3 milligrams for every 1 kilogram you weigh, injected once a week. This loading dose is for all patients.

For patients 12 years of age or older who weigh 40 kilograms or more, your doctor will prescribe one of the 3 doses beginning on week 5 as listed below:

- 1.5 milligrams for every 1 kilogram you weigh, injected once a week or,
- 3 milligrams for every 1 kilogram you weigh, injected once every 2 weeks or,
- 6 milligrams for every 1 kilogram you weigh, injected once every 4 weeks.

For patients 11 years of age or younger and any patient who weighs less than 40 kilograms, your doctor will prescribe one of the 2 doses beginning on week 5 as listed below:

- 1.5 milligrams for every 1 kilogram you weigh, injected once a week or
- 3 milligrams for every 1 kilogram you weigh, injected once every 2 weeks.

The dose of Hemlibra is dependent on your weight and your doctor should tell you how much to inject.

Instructions for Use (Transfer Needle with filter)

Transfer Needle with Filter

(For transfer of HEMLIBRA from vial to syringe)

Be sure that you read, understand and follow the Instructions for Use before injecting Hemlibra. Your healthcare provider should show you how to prepare, measure, and inject Hemlibra properly before you use it for the first time. Ask your healthcare provider if you have any questions.

Important Information:

- **Do not** inject yourself or someone else unless you have been shown how to by your healthcare provider.
- Make sure the name Hemlibra appears on the box and vial label.
- Before opening the vial, read the vial label to make sure you have the medicine strength(s) needed to give the dose prescribed by your healthcare provider. Depending on your dose, you may need to use more than 1 vial to give your total prescribed dose.
- Check the expiry date on the box and vial label. **Do not** use if the expiry date has passed.
- **Only use the vial once.** After you inject your dose, throw away any unused Hemlibra left in the vial. Do not save unused medicine in the vial for later use.
- **Only use the syringes, transfer needles with filter, and injection needles that your healthcare provider prescribes.**
- **Only use the syringes, transfer needles with filter and injection needles once. Throw away any used syringes and needles.**

- If your prescribed dose is more than 2 mL, you will need to administer more than one (1) subcutaneous injection of Hemlibra; contact your healthcare provider for the appropriate injection instructions.

- Do not inject the medicine intravenously.

Storing Hemlibra vials, needles and syringes:

- Keep the vial in the original box to protect the medicine from light.

- Keep the vials, needles and syringes out of the sight and reach of children. Store the vial in the refrigerator.

- **Do not** freeze.

- **Do not** shake the vial.

- Take the vial out of the refrigerator 15 minutes before use and allow it to reach room temperature (below 30°C) before preparing an injection.

- Once removed from the refrigerator, the unopened vial can be kept at room temperature for up to 7 days. After storage at room temperature unopened vials may be returned to the refrigerator. Cumulative storage time (total amount of time outside cold storage) at room temperature should not exceed 7 days.

- Discard vials that have been kept at room temperature for more than 7 days or exposed to temperatures above 30°C.

- Keep the transfer needle with filter, injection needle and syringe dry.

Inspecting the medicine and your supplies:

- Collect all supplies listed below to prepare and give your injection.

- **Check** the expiry date on the box, on the vial label and on the supplies listed below. **Do not use** if the expiry date has passed.

- **Do not use** the vial if:
  - the medicine is cloudy, hazy or coloured.
  - the medicine contains particles.
  - the cap covering the stopper is missing.

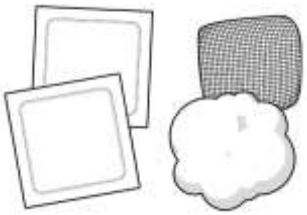
- Inspect the supplies for damage. **Do not use** if they appear damaged or if they have been dropped.
- Place the supplies on a clean, well-lit flat work surface.

INCLUDED IN THE BOX:

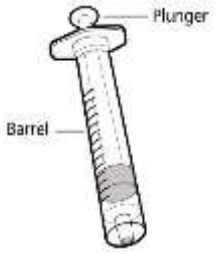
- **Vial containing the medicine**

- **Instructions for Use**

NOT INCLUDED IN THE BOX:

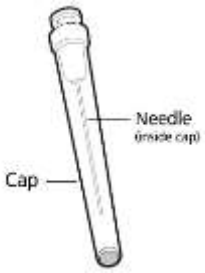


- **Alcohol wipes**
  Note: If you need to use more than 1 vial to inject your prescribed dose, you must use a new alcohol wipe for each vial.
- **Gauze**
- **Cotton Ball**



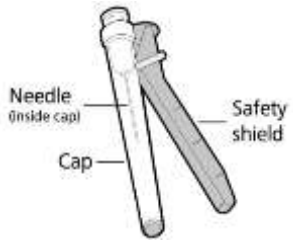
- **Syringe**
  Note: For injection amount up to 1 mL use a **1 mL syringe.**

  For injection amount between 1 mL and 2 mL use a **2 mL or 3 mL syringe.**



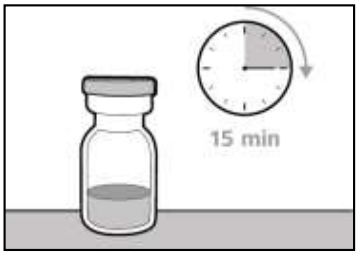
- **18G Transfer needle with 5 micrometer filter**
  Note: If you need to use more than 1 vial to inject your prescribed dose, you must use a new transfer needle with filter for each vial.
  Do not use the transfer needle with filter to inject medicine.

- **26G Injection Needle with safety shield**
  Do not use the injection needle to withdraw medicine from vial.



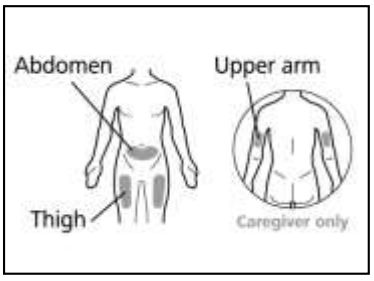
- **Sharps disposal container**

Get ready:



- Before use, allow the vial(s) to warm up to room temperature for about 15 minutes on a clean flat surface away from direct sunlight.
- Do not try to warm the vial by any other way.
- Wash your hands well with soap and water.

Selecting and preparing an injection site:



- Clean the chosen injection site area using an alcohol wipe.
- Let the skin dry for about 10 seconds. Do not touch, fan or blow on the cleaned area before your injection.

You can use your:

- Thigh (front and middle).
- Stomach area (abdomen), except for 5 cm around

the navel (belly button).
- Outer area of the upper arm (only if a caregiver is giving the injection).

- You should use a different injection site each time you give an injection, at least 2.5 cm away from the area you used for your previous injection.

- Do not inject into areas that could be irritated by a belt or waistband. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or the skin is broken.

Preparing the syringe for injection:

- Do not touch exposed needles or place them on a surface once the cap has been removed.

- Once the syringe has been filled with the medicine, it must be used immediately.

- Once the injection needle cap has been removed, the medicine in the syringe must be subcutaneously injected within 5 minutes. Do not use the syringe if the needle touches any surface

- **Throw away any used vial(s), needles, vial/injection needle caps and used syringes in a sharps/puncture-proof container.**

Important information after the injection:

- Do not rub the injection site after an injection.

- If you see drops of blood at the injection site, you can press a sterile cotton ball or gauze over the injection site for at least 10 seconds, until bleeding has stopped.

- If you have bruising (small area of bleeding under the skin), an ice pack can also be applied with gentle pressure to the site. If bleeding does not stop, please contact your healthcare provider.

Disposing of the medicine and supplies:

Important: Always keep the sharps disposal container out of reach of children.

- Put your used needles and syringes in a sharps disposal container straight away after use. Do not throw away any loose needles and syringes in your

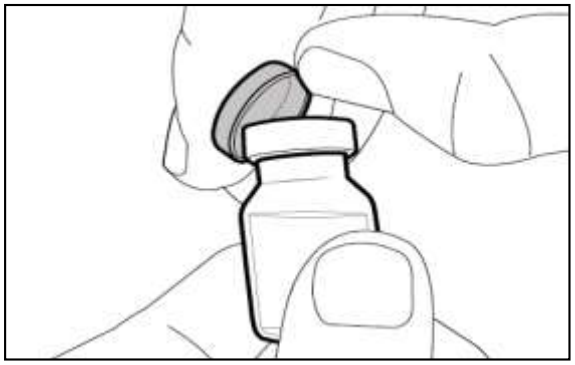
household waste.

- If you do not have a sharps disposal container, you may use a household container that is:
    - made of heavy-duty plastic.
    - can be closed with a tight-fitting, puncture resistant lid, without sharps being able to come out.
    - upright and stable during use.
    - leak-resistant.
    - properly labelled to warn of hazardous waste inside the container.

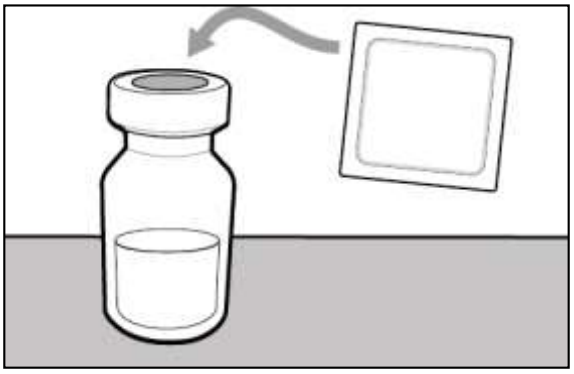
- When your sharps disposal container is almost full, you will need to follow your local guidelines for the right way to throw away your sharps disposal container.

- Do not throw away any used sharps disposal container in your household waste unless your local guidelines permit this. Do not recycle your used sharps disposal container.

Step 1. Remove vial cap and clean top

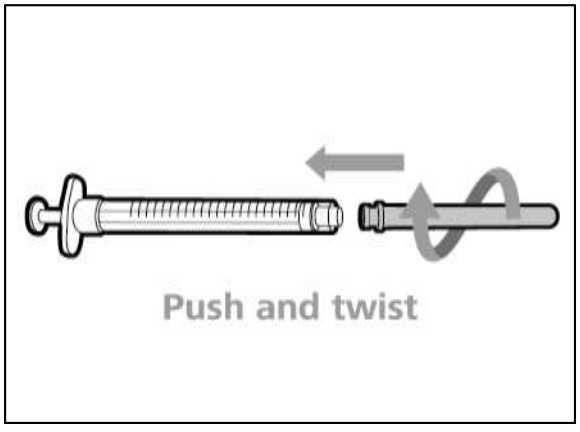


- Take the cap off the vial(s).

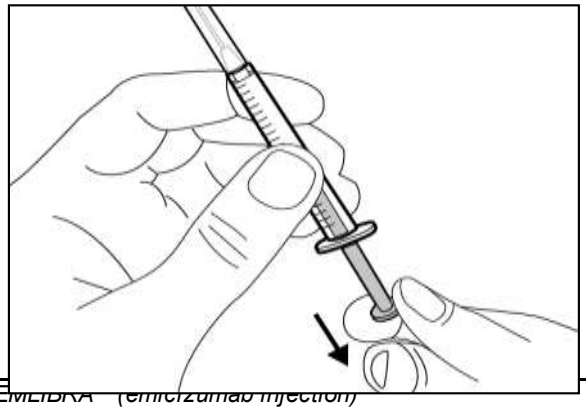


- Clean the top of the vial(s) stopper with an alcohol wipe.
- Throw away the vial cap(s) into the sharps disposal container.

Step 2. Attach transfer needle with filter to syringe

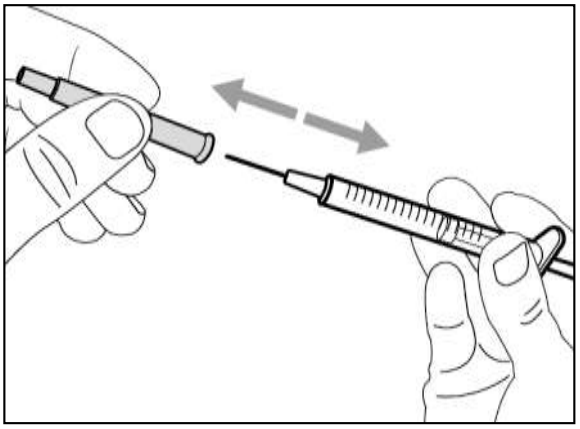


- **Push and twist the transfer needle with filter clockwise** on to the syringe until it is fully attached.



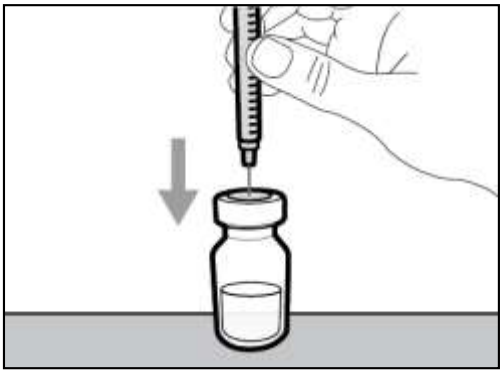
- Slowly pull back on the plunger and draw air into the syringe that is the same amount for your prescribed dose.

Step 3. Uncap transfer needle with filter

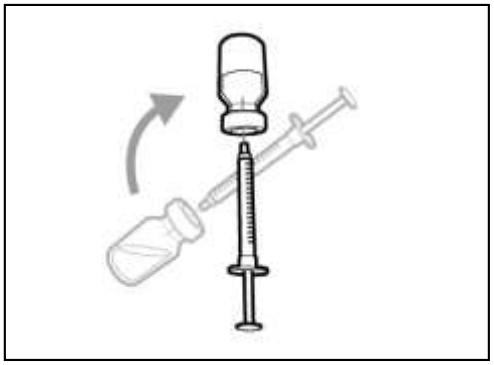


- Hold the syringe by the barrel with the transfer needle with filter pointing up.
- Carefully pull the transfer needle with filter cap straight off and away from your body. **Do not throw the cap away. Place the transfer needle with filter cap down on a clean flat surface.** You will need to recap the transfer needle with filter after transferring the medicine.
- **Do not touch** the needle tip or place it on a surface after the needle cap has been removed.

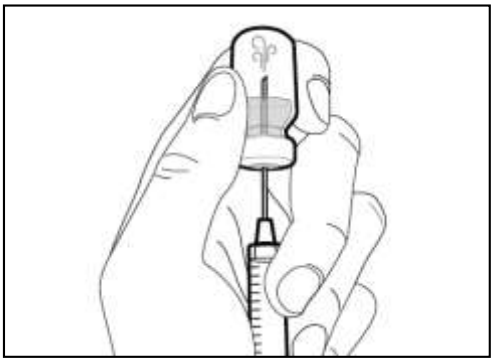
Step 4. Inject air into vial



- Keep the vial on the flat working surface and insert the transfer needle with filter and syringe straight down into the center of the vial stopper.

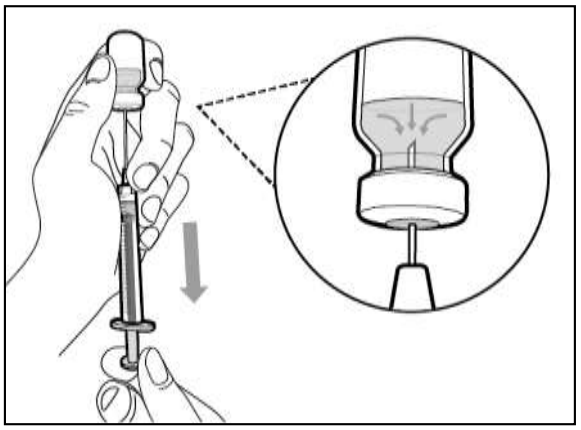


- Keep the needle in the vial and turn the vial upside down.



- With the needle pointing upwards, push on the plunger to inject the air from the syringe **above the medicine.**
- Keep your finger pressed down on the syringe plunger.
- **Do not** inject air into the medicine as this could create air bubbles in the medicine.

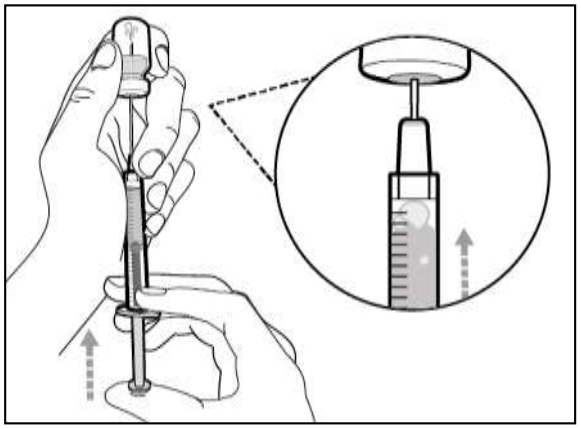
Step 5. Transfer medicine to syringe



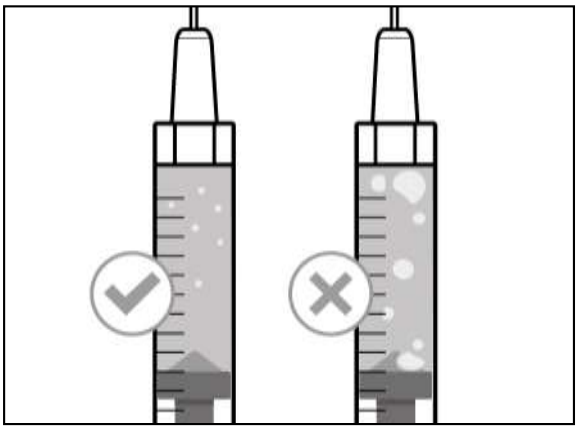
- Slide the tip of the needle down so that it is **within the medicine.**
- Slowly pull back the plunger to fill the syringe with more than the amount of medicine needed for your prescribed dose.
- Be careful not to pull the plunger out of the syringe.

Important: If your prescribed dose is more than the amount of medicine in the vial, **withdraw all of the medicine** and go to the "**Combining Vials**" section now.

Step 6. Remove air bubbles



- Keep the needle in the vial and check the syringe for larger air bubbles**.** Too large an air bubble can reduce the dose you receive.
- **Remove the larger air bubbles** by gently **tapping** the syringe barrel with your fingers until the air bubbles rise to the top of the syringe. Move the tip of the needle **above the medicine** and slowly push the plunger up to push the air bubbles out of the syringe.



- If the amount of medicine in the syringe is now at or below your prescribed dose, move the tip of the needle to **within the medicine** and slowly **pull** back the plunger until you have **more** than the amount of medicine needed for your **prescribed dose.**

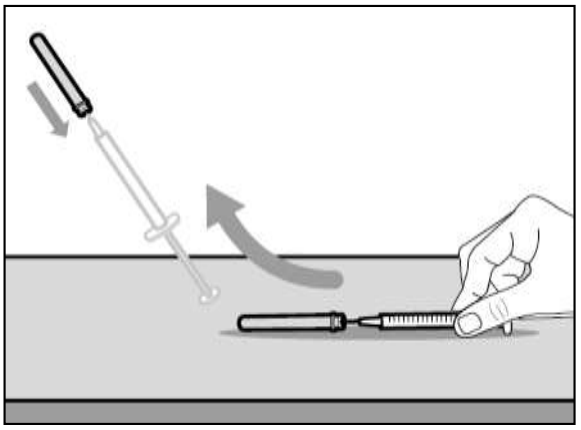
- Be careful not to pull the plunger out of the syringe.

- Repeat the steps above until you have removed the larger air bubbles.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving onto the next step. If you cannot remove all medicine, turn the vial upright to reach the remaining amount

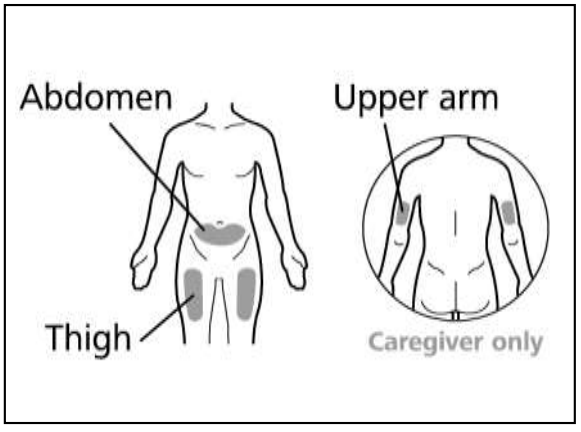
⚠**Do not** use the transfer needle with filter to inject medicine as this may cause harm such as pain and bleeding

Step 7. Recap transfer needle with filter



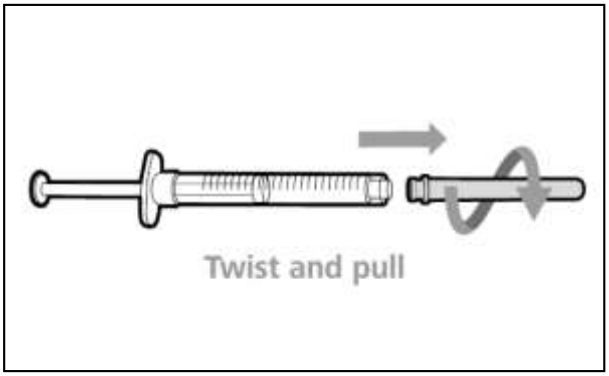
- Remove the syringe and transfer needle with filter from the vial.
- **Using one hand**, **slide** the transfer needle with filter into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle with filter cap towards the syringe to fully attach it with **one hand** to prevent accidentally sticking yourself with the needle.

Step 8. Clean injection site



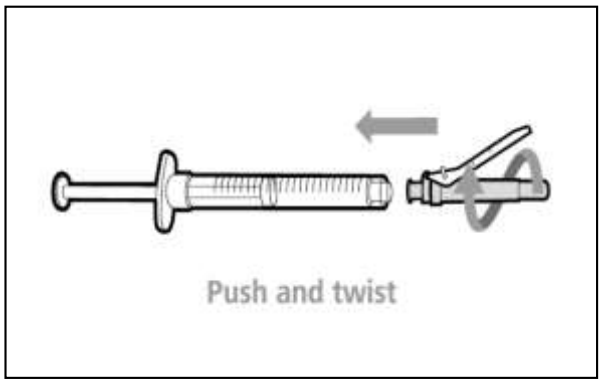
- Select and **clean** your injection site with an alcohol wipe.

Step 9. Remove transfer needle with filter



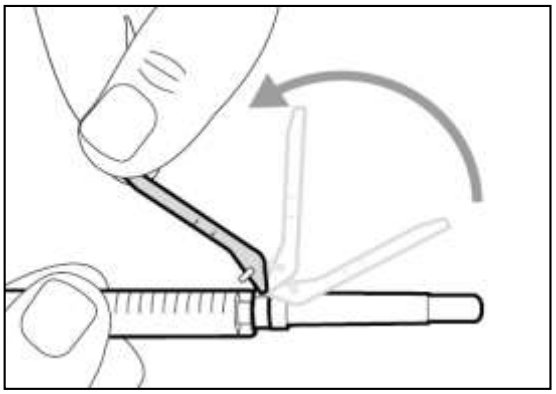
- Remove the transfer needle with filter from the syringe by twisting anticlockwise and gently pulling.
- Throw away the used transfer needle with filter into a sharps disposal container.

Step 10. Attach injection needle to syringe



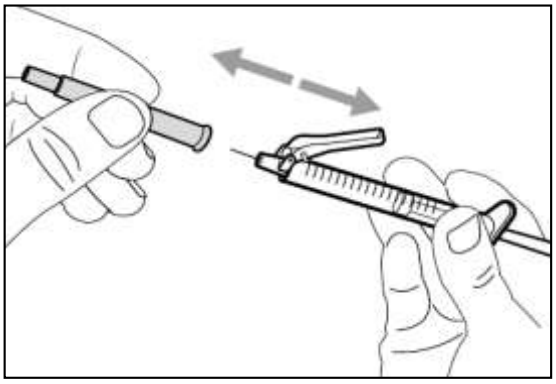
- Push and twist the injection needle clockwise onto the syringe until it is fully attached.

Step 11. Move safety shield



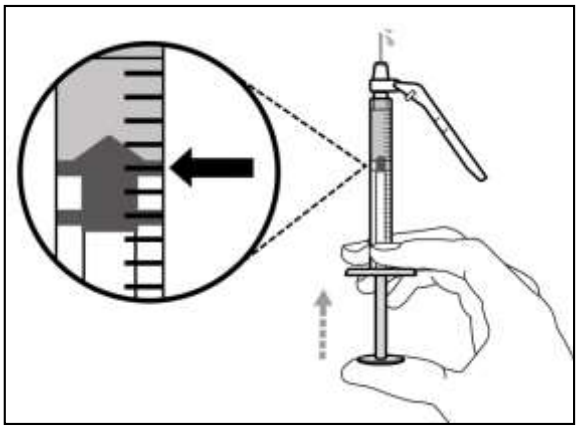
- Move the safety shield away from the needle and **towards** the syringe barrel.

Step 12. Uncap injection needle



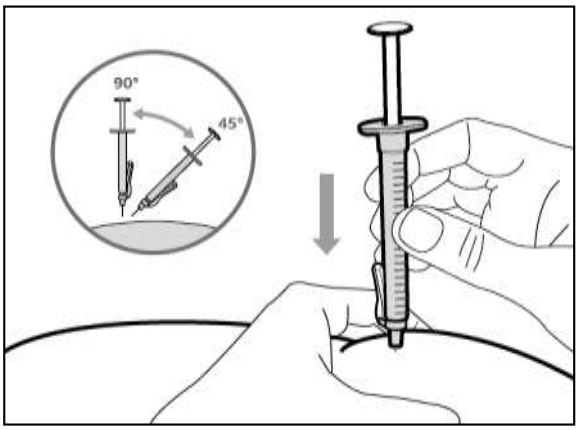
- Carefully pull the injection needle cap away from the syringe.
- Throw away the cap into a sharps disposal container.
- **Do not touch** the needle tip or allow it to touch any surface.
- After the injection needle cap has been removed, the medicine in the syringe must be injected within 5 minutes.

Step 13. Adjust plunger to prescribed dose



- Slowly push the plunger to your prescribed dose.
- Ensure the top rim of the plunger is in line with the mark on the syringe for your prescribed dose.

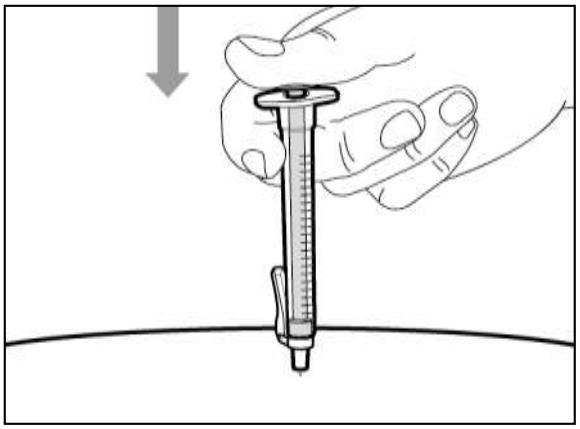
Step 14. Subcutaneous (under the skin) injection



- Pinch the selected injection site and fully insert the needle at a **45° to 90° angle** with a quick, firm action. **Do not** hold or push on the plunger while inserting the needle.
- Hold the position of the syringe and let go of the pinched injection site.

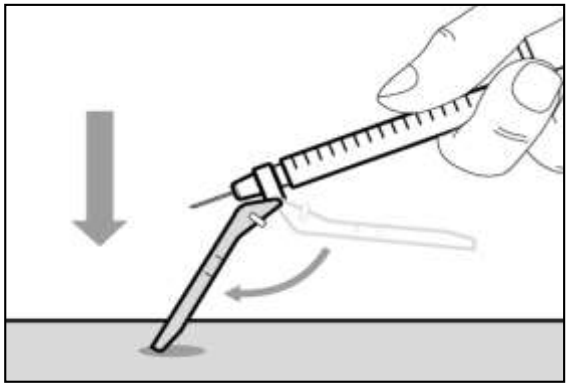
.

Step 15. Inject the medicine

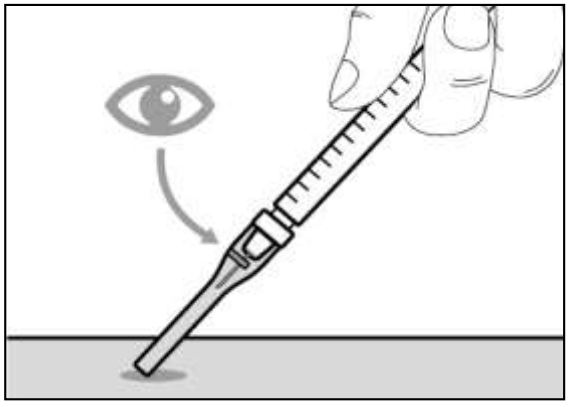


- Slowly inject all of the medicine by gently pushing the plunger all the way down.
- Remove the needle and syringe from the injection site at the same angle as inserted.

Step 16. Cover needle with safety shield

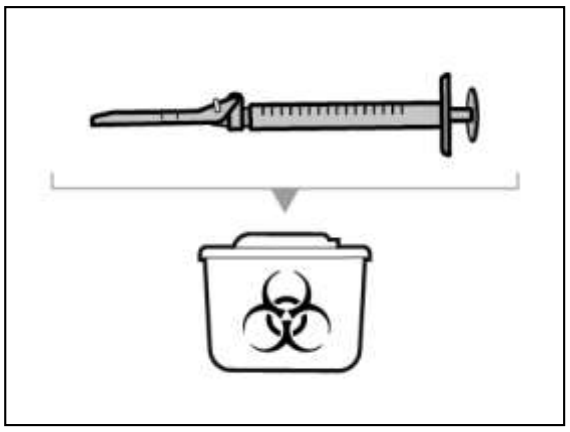


- Move the safety shield forward 90°, away from the syringe barrel.
- Holding the syringe with one hand, **press the safety shield down** against a flat surface with a firm, quick motion until you hear a “click”.



- If you do not hear a click, look to see that the needle is fully covered by the safety shield.
- Keep your fingers behind the safety shield and away from the needle at all times.
- **Do not** detach injection needle

Step 17. Throw away the syringe and needle.

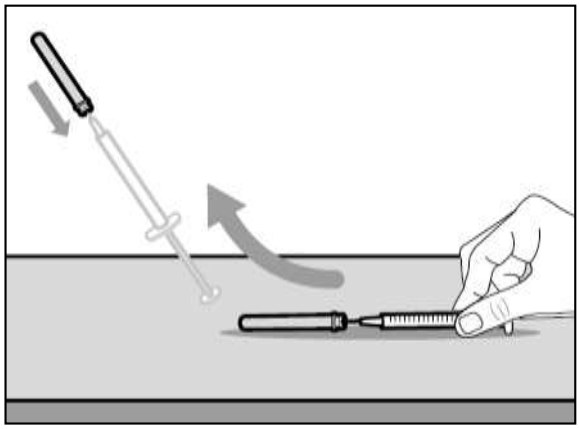


- Put **your** used needles and syringes in a sharps disposal container right away after use. For further information refer to the section “Disposing of the medicine and supplies”.
- **Do not** try to remove the used injection needle from the used syringe.
- **Do not recap** the injection needle with the cap.
- **Important:** Always keep the sharps disposal container out of reach of children.

Combining Vials

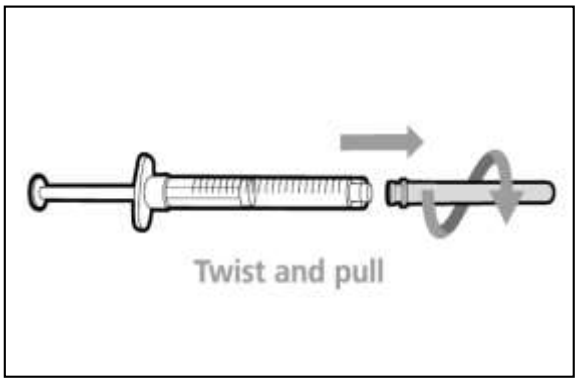
If you need to use more than 1 vial to get to your total prescribed dose, follow these steps after you have drawn up the medicine from the first vial:

Step A. Recap transfer needle with filter



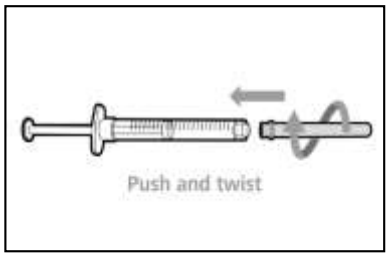
- Remove the syringe and transfer needle with filter from the first vial.
- **Using one hand**, slide the transfer needle with filter into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle with filter cap toward the syringe to fully attach it with **one hand** to prevent accidentally sticking yourself with the needle.

Step B. Remove transfer needle with filter



- Remove the transfer needle with filter from the syringe by twisting anticlockwise and gently pulling.
- Throw away the used transfer needle with filter into a sharps disposal container.

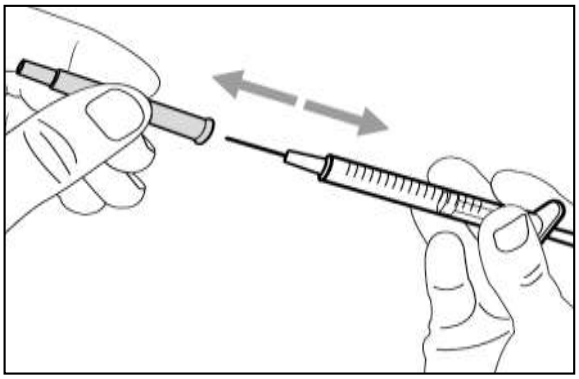
Step C. Attach a new transfer needle with filter to syringe



Note: You must use a new transfer needle with filter each time you withdraw medicine from a new vial.

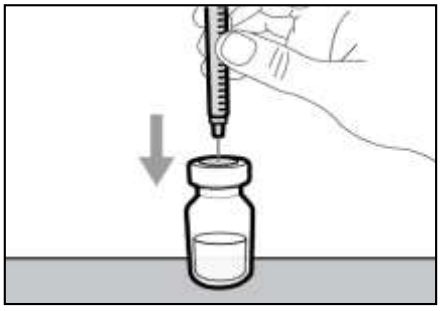
- Push and twist a **new** transfer needle with filter clockwise on to the syringe until it is fully attached.
- Slowly pull back the plunger and draw some air into the syringe.

Step D. Uncap transfer needle with filter

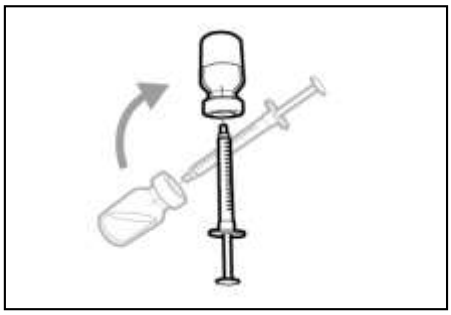


- Hold the syringe by the barrel with the transfer needle with filter cap pointing up.
- Carefully pull the transfer needle with filter cap straight off and away from your body. Do not throw the cap away. You will need to recap the transfer needle with filter after drawing up the medicine.
- **Do not touch** the needle tip.

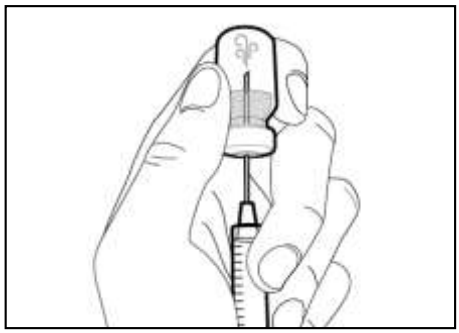
Step E. Inject air into vial



- With the new vial on the flat working surface, insert the new transfer needle with filter and syringe, straight down into the **center** of the vial stopper.

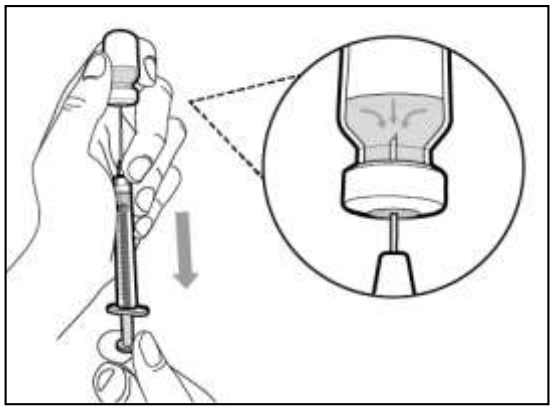


- Keep the transfer needle with filter in the vial and turn the vial upside down.



- With the needle pointing upwards, inject the air from the syringe **above the medicine.**
- Keep your finger pressed down on the syringe plunger.
- **Do not** inject air into the medicine as this could create air bubbles in the medicine.

Step F. Transfer medicine to syringe



- Slide the tip of the needle down so that it is **within the medicine**.
- Slowly pull back the plunger to fill the syringe barrel more than the amount of medicine needed for your prescribed dose.
- Be careful not to pull the plunger out of the syringe.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving onto the next steps. If you cannot remove all drug, turn the vial upright to reach the remaining amount

Do not use the transfer needle with filter to inject medicine as this may cause harm such as pain and bleeding.

Repeat steps A to F with each additional vial until you have more than your prescribed dose. Once completed, keep the transfer needle with filter inserted in the vial and return to Step 6. Continue with the remaining steps.

Overdose:

If you or your caregiver uses more Hemlibra than you are supposed to, tell your doctor immediately. This is because you may be at risk of developing side effects such as blood clots. Always use Hemlibra exactly as your doctor has told you, and check with your doctor, pharmacist or nurse if you are not sure.

If you think you have taken too much Hemlibra, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget your scheduled weekly injection, inject the forgotten dose as soon as possible before the day of the next scheduled dose. Then, continue to inject the medicine once a week as scheduled. Do not inject a double dose to make up for a forgotten dose.

If you are not sure what to do, ask your doctor, pharmacist or nurse.

Do not stop using Hemlibra without talking to your doctor. If you stop using Hemlibra, you may no longer be protected against bleeding.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

What are possible side effects from using Hemlibra?

These are not all the possible side effects you may feel when taking Hemlibra. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON <u>Thrombotic microangiopathy:</u> • confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, vague abdominal or back pain, feeling sick (nausea), being sick (vomiting) or urinating less – these symptoms may be signs of thrombotic microangiopathy.		✓	✓
<u>Blood clots (thromboembolism):</u> • swelling, warmth, pain or redness – these symptoms may be signs of a blood clot in a vein near the surface of the skin. • headache, numbness in your face, eye pain or swelling or vision impairment – these symptoms may be signs of a blood clot in a vein behind your eye. • blackening of the skin – this symptom may be a sign of severe damage to the skin tissue.		✓	✓

Other side effects with using Hemlibra

Very common: may affect 1 in 10 or more people

- a reaction in the area the injection was given (redness, itching, pain, swelling)
- headache

Common: may affect from 1 in 100 up to 1 in 10 people

- fever
- joint pain
- muscle aches
- diarrhea
- hives
- rash

Uncommon: may affect from 1 in 1000 up to 1 in 100 people

- blood clot in a vein behind your eye (cavernous sinus thrombosis)
- severe damage of the skin tissue (skin necrosis)
- blood clot in a vein near the surface of the skin (thrombophlebitis superficial)
- tiny blood clots that create damage to the small blood vessels (thrombotic microangiopathy)
- swelling under the skin (angioedema)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in a refrigerator (2°C to 8°C). Do not freeze. Do not shake.

Store in the original pack in order to protect from light.

Do not use this medicine after the expiry date listed on the carton and the vial label after "EXP". The expiry date refers to the last day of that month.

Once removed from the refrigerator, unopened vials may be kept at room temperature (below 30ºC) for up to 7 days. After storage at room temperature, unopened vials may be returned back to the refrigerator. The total length of time the medicine is stored at room tempera ture should not be more than 7 days.

Once transferred from the vial to the syringe, use Hemlibra straight away. Do not refrigerate the solution in the syringe.

Throw away any unused solution appropriately. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about Hemlibra:

- Talk to your healthcare professional
- Educational materials for Healthcare Professionals and patients are available from Hoffmann-La Roche Limited by calling 1-888-762-4388.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

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Hoffmann-La Roche Limited
Mississauga, ON L5N 5M8