CORE DATA SHEET 4.0

June 2018

HEMLIBRA™

INN: emicizumab

Information as set forth in this label only applies to HEMLIBRA™.

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1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

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

ATC code: B02BX06

1.2 TYPE OF DOSAGE FORM

Solution for injection.

1.3 ROUTE OF ADMINISTRATION

Subcutaneous injection.

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile product.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: emicizumab

HEMLIBRA solution for subcutaneous injection is a colorless to slightly yellow solution, adjusted to pH 6.0. HEMLIBRA is supplied in single-use colorless glass vials containing 30 mg/1 mL (30 mg/mL), 60 mg/0.4 mL (150 mg/mL), 105 mg/0.7 mL (150 mg/mL) or 150 mg/1 mL (150 mg/mL) of emicizumab.

For preparation, use and other handling recommendations, see section 4.2 Special Instructions for Use, Handling and Disposal.

Excipients: L-Histidine, L-Aspartic Acid, L-Arginine, Poloxamer 188, Water for Injection

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

HEMLIBRA is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

HEMLIBRA can be used in all age groups.

2.2 DOSAGE AND ADMINISTRATION

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders.

Treatment with bypassing agents should be discontinued the day before starting HEMLIBRA therapy (see section 2.4 Warnings and Precautions). FVIII prophylaxis may be continued for the first 7 days of HEMLIBRA treatment.

Recommended dosage (all patients)

The recommended loading dose is 3 mg/kg administered as a subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of either:

- 1.5 mg/kg once weekly, or
- 3 mg/kg every two weeks, or
- 6 mg/kg every four weeks.

The maintenance dose regimen should be selected based on physician and patient/caregiver dosing regimen preference to support adherence.

Method of administration

HEMLIBRA is for subcutaneous use only. HEMLIBRA should be administered using appropriate aseptic technique (see section 4.2 Special Instructions for Use, Handling and Disposal).

The injection should be restricted to the recommended injection sites: the abdomen, the upper outer arms and the thighs (see section 3.2 Pharmacokinetic Properties, Absorption). 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 section 2.6 Undesirable Effects, Clinical Trials). 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.

Duration of treatment

HEMLIBRA is intended for long-term prophylactic treatment.

Dosage adjustments during treatment

No dosage adjustments of HEMLIBRA are recommended.

Delayed or missed doses

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.

2.2.1 SPECIAL DOSAGE INSTRUCTIONS

Pediatric use

No dose adjustments are recommended in pediatric patients. Currently available data are described in sections 3.1.2 Clinical/Efficacy Studies and 3.2.5 Pharmacokinetics in Special Populations.

Geriatric use

No dose adjustments are recommended in patients ≥ 65 years of age (see section 3.2.5 Pharmacokinetics in Special Populations).

Renal impairment

No dose adjustments are recommended in patients with renal impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

Hepatic impairment

No dose adjustments are recommended in patients with hepatic impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

2.3 CONTRAINDICATIONS

HEMLIBRA is contraindicated in patients with known hypersensitivity to emicizumab or to any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 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.

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 section 2.6.1 Undesirable Effects, Clinical Trials). Treatment for the TMA events included supportive care with or without plasmapheresis and hemodialysis. Evidence of improvement was seen within one week following discontinuation of aPCC. This rapid clinical improvement is distinct from the usual clinical course observed in atypical hemolytic uremic syndrome and classic TMAs

such as thrombotic thrombocytopenic purpura (see section 2.6.1 Undesirable Effects, Clinical Trials).

Patients receiving HEMLIBRA prophylaxis should be monitored for the development of TMA when administering aPCC. The physician should immediately discontinue aPCC and interrupt HEMLIBRA therapy if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Physicians and patients/caregivers should weigh the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of TMA on a case-by-case basis. In case a bypassing agent is indicated in a patient receiving HEMLIBRA prophylaxis, see subsection below for dosing recommendations for the use of bypassing agents.

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 section 2.6.1 Undesirable Effects, Clinical Trials). No cases required anticoagulation therapy, which is distinct from the usual treatment of thrombotic events. Evidence of improvement or resolution was seen after discontinuation of aPCC (see section 2.6.1 Undesirable Effects, Clinical Trials).

Patients receiving HEMLIBRA prophylaxis should be monitored for the development of thromboembolism when administering aPCC. The physician 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. Physicians 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 subsection below for dosing recommendations for the use of bypassing agents.

Guidance on the use of bypassing agents in patients receiving HEMLIBRA prophylaxis

Treatment with bypassing agents should be discontinued the day before starting HEMLIBRA therapy.

Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required, while receiving HEMLIBRA prophylaxis.

HEMLIBRA increases the patient's 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 TMA or thrombotic events were observed with use of activated recombinant human FVII (rFVIIa) alone in patients receiving HEMLIBRA prophylaxis.

Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of HEMLIBRA prophylaxis (see section 3.2.4 Pharmacokinetic Properties, Elimination).

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 1 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 1 below (see section 2.8 Interactions with Other Medicinal Products and Other Forms of Interaction).

Table 1 Coagulation Test Results Affected and Unaffected by HEMLIBRA

Results Affected by HEMLIBRA	Results Unaffected by HEMLIBRA
Activated partial thromboplastin time (aPTT) Bethesda assays (clotting-based) for FVIII inhibitor titers One-stage, aPTT–based, single-factor assays (e.g. FVIII activity) aPTT-based activated protein C resistance (APC-R) Activated clotting time (ACT)	Bethesda assays (bovine chromogenic) for FVIII inhibitor titers Thrombin time (TT) One-stage, prothrombin time (PT)-based, single-factor assays Chromogenic-based single-factor assays other than FVIII* 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 section 2.8 Interactions with Other Medicinal Products and Other Forms of Interaction.	

2.4.2 Drug Abuse and Dependence

HEMLIBRA does not have the potential for abuse and dependence.

2.4.3 Ability to Drive and Use Machines

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.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Fertility

No text (see section 3.3.3 Preclinical Safety, Impairment of Fertility).

Pregnancy testing

No text.

Contraception

Women of childbearing potential receiving HEMLIBRA should use effective contraception during, and for at least 6 months after cessation of HEMLIBRA treatment (see section 3.2.4 Pharmacokinetic Properties, Elimination).

2.5.2 PREGNANCY

There are no clinical studies of HEMLIBRA use in pregnant women. Animal reproduction studies have not been conducted with HEMLIBRA. 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.

Labor and delivery

The safe use of HEMLIBRA during labor and delivery has not been established.

2.5.3 LACTATION

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.

2.5.4 PEDIATRIC USE

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

These four clinical studies included a total of 107 pediatric patients in the following age groups: 47 adolescents (12 years to < 18 years), 55 children (2 years to < 12 years) and 5 infants (1 month to < 2 years) (see sections 3.1.2 Clinical/Efficacy Studies).

Safety and efficacy results were consistent with those observed for adults (see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations, Clinical Trials).

The steady-state plasma trough concentrations of emicizumab were comparable in adult and pediatric patients at equivalent weight-based doses (3.2.5 Pharmacokinetics in Special Populations).

2.5.5 GERIATRIC USE

The safety and efficacy of HEMLIBRA have not been specifically tested in a geriatric population. Clinical studies of HEMLIBRA included 13 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 (3.2.5 Pharmacokinetics in Special Populations).

2.5.6 RENAL IMPAIRMENT

The safety and efficacy of HEMLIBRA have not been specifically tested in patients with renal impairment. There are limited data available on the use of HEMLIBRA in patients with mild to moderate renal impairment. No data are available on the use of HEMLIBRA in patients with severe renal impairment. HEMLIBRA is a monoclonal antibody and is cleared via catabolism rather than by renal excretion and a change in dose is not expected to be required for patients with renal impairment (see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations).

2.5.7 HEPATIC IMPAIRMENT

The safety and efficacy of HEMLIBRA have not been specifically tested in patients with hepatic impairment. Patients with mild and moderate hepatic impairment were included in clinical trials. No data are available on the use of HEMLIBRA in patients with severe hepatic impairment. HEMLIBRA is a monoclonal antibody and is cleared via catabolism rather than by hepatic metabolism and a change in dose is not expected to be required for patients with hepatic impairment (see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations).

2.6 UNDESIRABLE EFFECTS

2.6.1 CLINICAL TRIALS

The following adverse drug reactions (ADRs) are based on pooled data from four phase III clinical trials (three adult and adolescent studies [HAVEN 1, HAVEN 3, and HAVEN 4] and a pediatric study [HAVEN 2]), in which a total of 373 male patients with hemophilia A received at least one dose of HEMLIBRA as routine prophylaxis. Two hundred and sixty-six (71%) patients were adults (≥ 18 years), 47 (13%) were adolescents (≥ 12 to < 18 years), 55 (15%) were children (≥ 2 to < 12 years) and five

were infants (≥ 1 month to < 2 years). The median duration of exposure across the studies was 34.1 weeks (range: 0.1 to 94.3 weeks).

Three patients (0.8%) 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 the pooled phase III clinical trials in patients who received HEMLIBRA are listed by MedDRA system organ class (see Table 2 below). The corresponding frequency categories for each ADR are based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100).

Table 2 Summary of Adverse Drug Reactions from Pooled Clinical Trials with HEMLIBRA

System Organ Class ADR (preferred term, MedDRA)	Number of patients (N = 373)	Percentage of patients	Frequency
General disorders and administration site conditions			
Injection site reactions	77	21%	Very common
Pyrexia	22	6%	Common
Nervous system disorders			
Headache	52	14%	Very common
Gastrointestinal disorders			
Diarrhea	19	5%	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	58	16%	Very common
Myalgia	13	4%	Common
Blood and Lymphatic system disorders			
Thrombotic microangiopathy	3	<1%	Uncommon
Infections and Infestations			
Cavernous sinus thrombosis	1	<1%	Uncommon
Skin and subcutaneous tissue disorders			
Skin necrosis	1	<1%	Uncommon
Vascular Disorders			
Thrombophlebitis superficial	1	<1%	Uncommon

Description of selected adverse drug reactions

The most serious adverse drug reactions reported from the pooled phase III clinical trials with HEMLIBRA were TMA and thrombotic events, including cavernous sinus thrombosis and superficial vein thrombosis contemporaneous with skin necrosis (see below and section 2.4 Warnings and Precautions).

Thrombotic microangiopathy

In the pooled phase III clinical trials, thrombotic microangiopathy events were reported in <1% of patients (3/373) and in 9.7% of patients (3/31) who received at least one dose of aPCC. Each patient was reported to have received on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more while receiving HEMLIBRA prophylaxis prior to the development of TMA events (presenting with thrombocytopenia, microangiopathic hemolytic anemia and acute kidney injury, without severe deficiencies in ADAMTS13 activity). One patient resumed HEMLIBRA following resolution of TMA without recurrence (see section 2.4 Warnings and Precautions).

Thrombotic events

In the pooled phase III clinical trials, serious thrombotic events were reported in <1% of patients (2/373) and in 6.5% of patients (2/31) who received at least one dose of aPCC. Each patient was reported to have received on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more while receiving HEMLIBRA prophylaxis, prior to the development of the thrombotic events. One patient resumed HEMLIBRA following resolution of the thrombotic event without recurrence (see section 2.4 Warnings and Precautions).

Characterization of aPCC Treatment (in the pooled phase III clinical trials)

There were 82 instances of aPCC treatment*, of which 8 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 8 instances were associated with thrombotic events and three of the 8 instances were associated with TMA (see Table 3). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment. Of all instances of aPCC treatment, 68% consisted of a single infusion ≤ 100 U/kg.

Table 3 Characterization of aPCC Treatment* in the Pooled Phase III 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[a, b, b, 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

[b] Thrombotic microangiopathy

Injection site reactions

Injection site reactions (ISRs) were reported very commonly (21 %) from clinical trials. All ISRs observed in the HEMLIBRA clinical trials were reported as being non-serious

and mild to moderate in intensity, and 95% resolved without treatment. The most commonly reported ISR symptoms were injection site erythema (11%); injection site pain (4%) and injection site pruritus (3%).

2.6.2 POST MARKETING

No data to report.

2.7 OVERDOSE

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.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Clinical experience suggests that a drug interaction exists with HEMLIBRA and aPCC (see sections 2.4 Warnings and Precautions and 2.6.1 Undesirable Effects, Clinical Trials).

There is a possibility for hypercoagulability with rFVIIa or FVIII with HEMLIBRA based on preclinical experiments. Emicizumab increases coagulation potential, therefore the coagulation factor dose required to achieve hemostasis may be lower than when used without HEMLIBRA prophylaxis.

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 section 2.4 Warnings and Precautions, Table 1). 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 section 3.2.4 Pharmacokinetic Properties, Elimination).

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 MECHANISM OF ACTION

Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is 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.

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.

3.1.2 CLINICAL / EFFICACY STUDIES

The efficacy of HEMLIBRA for routine prophylaxis in patients with hemophilia A with or without inhibitors to FVIII was evaluated in four clinical studies (three adult and adolescent studies [HAVEN 3, HAVEN 1, and HAVEN 4] and a pediatric study [HAVEN 2]).

Clinical Studies in Adult and Adolescent Patients

HAVEN 3

The HAVEN 3 study was a randomized, multicenter, open-label, phase III clinical study in 152 adult and adolescent 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. For Arms A and B dose up-titration to 3 mg/kg weekly was allowed after 24 weeks for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). Arm D patients could up-titrate after the second qualifying bleed. At the time of the analysis, five patients underwent up-titration of their maintenance dose.

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 (see Table 4). 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 (see Table 5), as well as assessing patient-reported health-related quality of life (HRQoL) (see Table 11). Patient treatment preference was also assessed using a preference survey.

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) prior to enrollment (see Table 6). 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.

HAVEN 1

The HAVEN 1 study was a randomized, multicenter, open-label clinical study in 109 adolescent and adult males (aged ≥ 12 years old and ≥ 40 kg) with hemophilia A with factor VIII 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, C, and D) — 3 mg/kg once weekly for 4 weeks followed by 1.5 mg/kg once weekly thereafter — or no prophylaxis (Arm B). Patients randomized to Arm B could switch to HEMLIBRA prophylaxis after completing at least

24 weeks without prophylaxis. Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on HEMLIBRA prophylaxis for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). During the study, two patients underwent up-titration of their maintenance dose to 3 mg/kg once weekly.

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).

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled in Arm C to receive HEMLIBRA prophylaxis. Seven patients previously treated with episodic ("on-demand") bypassing agents who had participated in the NIS prior to enrollment but were unable to enroll into HAVEN 1 prior to the closure of Arms A and B were enrolled in Arm D to receive HEMLIBRA prophylaxis.

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) (see Table 4). 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 (see Table 7), as well as assessing patients' HRQoL and health status (see Tables 12 and 13).

The efficacy of weekly HEMLIBRA prophylaxis compared with previous prophylactic bypassing agents was also evaluated in patients who had participated in the NIS prior to enrollment (Arms C) (see Table 8). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity as that used in HAVEN 1.

HAVEN 4

HEMLIBRA was investigated in a single arm, multicenter, phase III 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. Patients received HEMLIBRA prophylaxis – 3 mg/kg once weekly for four weeks followed by 6 mg/kg 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 (see Table 4). 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 (see Table 10) as well as assessing patients' HRQoL (see Table 14). Patient treatment preference was also assessed using a preference survey.

Adult and Adolescent Efficacy Results

The efficacy results of HEMLIBRA prophylaxis with respect to rate of treated bleeds are shown in Table 4.

Table 4 HAVEN 3, HAVEN 1 and HAVEN 4: Annualized Bleed Rate (Treated Bleeds – Primary Endpoint) with HEMLIBRA Prophylaxis in Patients ≥ 12 Years of Age with or without Factor VIII Inhibitors

Endpoint	HAVEN 3			HAVEN 1		HAVEN 4
	Arm C: No Prophylaxis (N = 18)	Arm A: HEMLIBRA 1.5 mg/kg weekly (N = 36)	Arm B: HEMLIBRA 3.0 mg/kg every 2 weeks (N = 35)	Arm B: No Prophylaxis (N = 18)	Arm A: HEMLIBRA 1.5 mg/kg weekly (N = 35)	HEMLIBRA 6 mg/kg every 4 weeks (N = 41)
Median Efficacy Period (weeks)	24.0	29.6	31.3	24.0	29.3	25.6
Treated Bleeds						
ABR (95% CI) [a]	38.2 (22.9; 63.8)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)	23.3 (12.3; 43.9)	2.9 (1.7; 5)	2.4 (1.4; 4.3)
% reduction vs episodic treatment (95% CI), p-value	NA	96% (92.5%; 98.0%), < 0.0001	97% (93.4%; 98.3%), < 0.0001	NA	87% (72.3%; 94.3%), < 0.0001	NA
% patients with 0 bleeds (95% CI)	0.0 (0.0; 18.5)	55.6 (38.1; 72.1)	60.0 (42.1; 76.1)	5.6 (0.1; 27.3)	62.9 (44.9; 78.5)	56.1 (39.7; 71.5)
% patients with 0-3 bleeds (95% CI)	5.6 (0.1; 27.3)	91.7 (77.5; 98.2)	94.3 (80.8; 99.3)	11.1 (1.4; 34.7)	85.7 (69.7; 95.2)	90.2 (76.9; 97.3)
Median ABR (IQR)	40.4 (25.3; 56.7)	0 (0; 2.5)	0 (0; 1.9)	18.8 (13.0; 35.1)	0 (0; 3.7)	0 (0; 2.1)

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

HAVEN 3

The efficacy results of HEMLIBRA prophylaxis compared with no prophylaxis with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown below in Table 5.

Table 5 HAVEN 3: Annualized Bleed Rate with HEMLIBRA Prophylaxis Arm versus No Prophylaxis Arm 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
% 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)
Treated Target Joint Bleeds			
ABR (95% CI) [a]	13.0 (5.2; 32.3)	0.6 (0.3; 1.4)	0.7 (0.3; 1.6)
% reduction (95% CI), p-	NA	95% (85.7%; 98.4%),	95% (85.3%; 98.2%),

value		<0.0001	<0.0001
% patients with 0 bleeds (95% CI)	27.8 (9.7; 53.5)	69.4 (51.9; 83.7)	77.1 (59.9; 89.6)
Median ABR (IQR)	12.8 (0; 39.1)	0 (0; 1.4)	0 (0; 0)

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.

In the HAVEN 3 clinical study intra-patient analysis, HEMLIBRA prophylaxis resulted in a statistically significant ($p<0.0001$) reduction (68%) in bleed rate for treated bleeds compared with previous FVIII prophylaxis collected in the NIS prior to enrollment (see Table 6).

Table 6 HAVEN 3: Intra-Patient Comparison of Annualized Bleed Rate (Treated Bleeds) with HEMLIBRA Prophylaxis versus Previous FVIII Prophylaxis

Endpoint	**Arm D_{NIS}: Previous FVIII Prophylaxis (N = 48)**	**Arm D: HEMLIBRA 1.5 mg/kg weekly (N = 48)**
Median Efficacy Period (weeks)	30.1	33.7
Treated Bleeds		
ABR (95% CI) [a]	4.8 (3.2; 7.1)	1.5 (1; 2.3)
% reduction (95% CI), p-value	68% (48.6%; 80.5%), <0.0001	
% patients with zero bleeds (95% CI)	39.6 (25.8; 54.7)	54.2 (39.2; 68.6)
Median ABR (IQR)	1.8 (0; 7.6)	0 (0; 2.1)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Based on negative binomial regression model.

HAVEN 1

The efficacy results of HEMLIBRA prophylaxis compared with no prophylaxis with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 7.

Table 7 HAVEN 1: Annualized Bleed Rate with HEMLIBRA Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age with Factor VIII Inhibitors

Endpoint	Arm B: No Prophylaxis	Arm A: HEMLIBRA 1.5 mg/kg weekly
	N=18	N=35
Treated Bleeds		
ABR (95% CI)	23.3 (12.33; 43.89)	2.9 (1.69; 5.02)
% 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 (12.97;35.08)	0 (0; 3.73)
All Bleeds		
ABR (95% CI)	28.3 (16.79; 47.76)	5.5 (3.58; 8.60)
% 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)
Median ABR (IQR)	30.2 (18.3; 39.4)	2 (0; 9.9)
Treated Spontaneous Bleeds		
ABR (95% CI)	16.8 (9.94; 28.30)	1.3 (0.73; 2.19)
% 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)
Median ABR (IQR)	15.2 (6.6; 30.4)	0 (0; 3.3)
Treated Joint Bleeds		
ABR (95% CI)	6.7 (1.99; 22.42)	0.8 (0.26; 2.20)
% reduction (95% CI), p-value	89% (48%, 97.5%)), 0.0050	
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	85.7 (69.7; 95.2)
Median ABR (IQR)	1 (0; 14.4)	0 (0; 0)
Treated Target Joint Bleeds		
ABR (95% CI)	3.0 (0.96; 9.13)	0.1 (0.03; 0.58)
% 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)
Median ABR (IQR)	1 (0; 6.5)	0 (0; 0)

Confidence interval come from 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.
Includes data before up-titration only, for patients whose dose was up-titrated.
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.

Additional analyses for HAVEN 1 to assess long term control of bleeds with HEMLIBRA prophylaxis were conducted using 12-week treatment intervals up to week 72. When ABR for treated bleeds was assessed over 12-week intervals the mean ABRs decreased over time and the improvement was sustained up to week 72, while the median remained consistently at zero (see Table 8). These data demonstrate the long term

efficacy of HEMLIBRA prophylaxis. The mean and median calculated ABRs for treated bleeds are shown in Table 8.

Table 8 HAVEN 1: Annualized Bleed Rate with HEMLIBRA Prophylaxis per 12-Week Intervals in Patients ≥ 12 Years of Age with Factor VIII Inhibitors

	Time Interval from Start of HEMLIBRA treatment (Weeks)					
	1 – 12 (N = 109)	13 – 24 (N = 108)	25 – 36 (N = 93)	37 – 48 (N = 93)	49 – 60 (N = 57)	61 – 72 (N = 42)
Treated Bleeds						
Mean ABR (95% CI)	3.9 (1.1, 10.2)	2.2 (0, 7.6)	0.9 (0, 5.5)	0.4 (0, 4.4)	0.5 (0, 4.7)	0.6 (0, 4.9)
Median ABR (IQR)	0 (0; 4.4)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)

In the HAVEN 1 clinical study intra-patient analysis, HEMLIBRA prophylaxis resulted in a statistically significant ($p = 0.0003$) reduction (79%) in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrollment (see Table 9).

Table 9 HAVEN 1: Intra-Patient Comparison of Annualized Bleed Rate (Treated Bleeds) with HEMLIBRA Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	Arm C_{NIS}: Previous Bypassing Agent Prophylaxis	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 (11.08; 22.29)	3.3 (1.33; 8.08)
% 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 (5.73; 24.22)	0.0 (0.00; 2.23)

Confidence interval come from 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.
Includes data before up-titration only, for patients whose dose was up-titrated.
Treated bleeds: bleeds treated with bypassing agents.
Bleed definitions adapted based on ISTH criteria.
ABR= Annualized Bleed Rate; CI= confidence interval; IQR=interquartile range, 25th percentile to 75th percentile.

HAVEN 4

Efficacy results for the HAVEN 4 clinical study are summarized below. Forty-one patients ≥12 years old were evaluated for efficacy with a median observation time of 25.6 weeks (range: 24.1 – 29.4 weeks). The efficacy results of HEMLIBRA prophylaxis every four weeks with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 10.

Table 10 HAVEN 4: Annualized Bleed Rate with HEMLIBRA Prophylaxis in Patients ≥ 12 Years of Age with or without Factor VIII Inhibitors

	HEMLIBRA 6 mg/kg Q4W		
Endpoints	**[a]ABR (95% CI)**	**[b]Median ABR (IQR)**	**% Zero Bleeds (95% CI)**
N =	41	41	41
Treated Bleeds	2.4 (1.4; 4.3)	0 (0; 2.1)	56.1 (39.7; 71.5)
All Bleeds	4.5 (3.1; 6.6)	2.1 (0; 5.9)	29.3 (16.1; 45.5)
Treated Spontaneous Bleeds	0.6 (0.3; 1.5)	0 (0; 0)	82.9 (67.9; 92.8)
Treated Joint Bleeds	1.7 (0.8; 3.7)	0 (0; 1.9)	70.7 (54.5; 83.9)
Treated Target Joint Bleeds	1.0 (0.3; 3.3)	0 (0; 0)	85.4 (70.8; 94.4)

[a]Calculated with negative binomial regression (NBR) model.
[b]Calculated ABR
Bleed definitions adapted based on ISTH criteria.
Treated bleeds: bleeds treated with FVIII or rFVIIa
All bleeds: bleeds treated and not treated with FVIII or rFVIIa.
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

Adults and Adolescents Health-Related Outcome Measures

The HAVEN adult and adolescent clinical studies evaluated patient-reported outcomes with several measures. The Haemophilia-Specific Quality of Life (Haem-A-QoL) questionnaire for adults (≥ 18 years) and its adolescent version (Haemo-QoL-SF, for 8 to <18 years) assessed hemophilia-related quality of life in patients. For the Haem-A-QoL and Haemo-QoL-SF, the Physical Health Score (i.e., painful swellings, presence of joint pain, pain with movement, difficulty walking far and needing more time to get ready) and Total Score (summary of all scores) were protocol defined endpoints of interest. To measure change in health status, the Index Utility Score (IUS) and the Visual Analog Scale (VAS) from the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) was examined.

In HAVEN 3 and 4, an assessment of patient preference for treatment, the Emicizumab Preference Survey (EmiPref), was used.

Adult and Adolescent Health-Related Outcomes Results

HAVEN 3 Health-Related Outcomes

In HAVEN 3, health-related quality of life (HRQoL) for patients aged ≥ 18 years was evaluated at week 25 based on the Haem-A-QoL questionnaire for adults. The Haem-A-QoL is a valid and reliable measure of HRQoL (see Table 11).

Table 11 HAVEN 3: Change in Haem-A-QoL Physical Health Score in Patients (≥ 18 Years of Age) with No Prophylaxis versus HEMLIBRA Prophylaxis at Week 25

Haem-A-QoL Scores at week 25	Arm C: No Prophylaxis (N = 13[a])	Arm A: HEMLIBRA 1.5 mg/kg weekly (N =34[a])	Arm B: HEMLIBRA 3.0 mg/kg every 2 weeks (N = 29[a])
Physical Health Score (range 0 to 100)[b]			
Adjusted mean[c]	44.3	31.8	28.4
Difference in adjusted means (95% CI)		12.5 (-2; 27)	16 (1.2, 30.8)

[a] Number of patients ≥ 18 years who completed the Haem-A-QoL questionnaire at both baseline and week 25.
[b] Lower scores are reflective of better functioning.
[c] Adjusted for baseline, and baseline by treatment group interaction
Includes data before up-titration only, for patients whose dose was up-titrated.

HAVEN 1 Health-Related Outcomes

In HAVEN 1, HRQoL for patients aged ≥ 18 years was evaluated at week 25 based on the Haem-A-QoL questionnaire for adults (see Table 12).

Table 12 HAVEN 1: Change in Haem-A-QoL 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: No Prophylaxis (N=16)	Arm A: HEMLIBRA 1.5 mg/kg weekly (N=31)
Total Score (range 0 to 100)		
n	14[a]	25[a]
Adjusted mean	43.21	29.2
Difference in adjusted means (95% CI)	14.01 (5.56, 22.45)	
p-value	0.0019	
Physical Health Score (range 0 to 100)		
n	14[a]	25[a]
Adjusted mean	54.17	32.61
Difference in adjusted means (95% CI)	21.55 (7.89, 35.22)	
p-value	0.0029	

Arm B: includes no prophylaxis period only.
Includes data before up-titration only, for patients whose dose was up-titrated.
Patients exposed to emicizumab started with a loading dose of 3 mg/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 1 Health Status Outcomes

In HAVEN 1, patients' health status was assessed according to EQ-5D-5L. EQ-5D-5L is a valid and reliable measure of health status (see Table 13).

Table 13 HAVEN 1: EQ-5D-5L Scores at Week 25

EQ-5D-5L Scores at week 25	Arm B: No Prophylaxis	Arm A: HEMLIBRA 1.5 mg/kg weekly
	N=18	N=35
Visual Analogue Scale (VAS)		
n	16	29
Adjusted mean	74.36	84.08
Difference in adjusted means (95% CI)	-9.72 (-17.62, -1.82)	
p-value	0.0171	
Index Utility Score		
n	16	29
Adjusted mean	0.65	0.81
Difference in adjusted means (95% CI)	-0.16 (-0.25, -0.07)	
p-value	0.0014	

Arm B: includes no prophylaxis period only.
Includes data before up-titration only, for patients whose dose was up-titrated.
Patients exposed to emicizumab started with a loading dose of 3 mg/kg/week for 4 weeks
Higher scores indicate better quality of life.
Clinically meaningful difference: VAS: 7 points; Index Utility Score: 0.07 points

HAVEN 4 Health-Related Outcomes

In HAVEN 4, HRQoL for patients aged ≥ 18 years was evaluated at week 25 based on the Haem-A-QoL questionnaire for adults (see Table 14).

Table 14 HAVEN 4: Change from Baseline to Week 25 in Haem-A-QoL in the Physical Health Score of Patients (≥ 18 Years of Age) following Treatment with HEMLIBRA Prophylaxis

	Haem-A-QoL
Physical Health Score (range 0 to 100)[a]	
Mean baseline score (95% CI) (n = 37)	47.6 (39.19 - 55.95)
Mean change from baseline (95% CI) (n = 37)	-15.1 (-22.4; -7.8)

[a] Lower scores (negative change scores) are reflective of better functioning.

HAVEN 3 and 4 Patient Preference

In HAVEN 3 and HAVEN 4, patients who received HEMLIBRA (once weekly, every two weeks or every four weeks) reported whether they preferred subcutaneous HEMLIBRA, their prior IV treatment or had no preference at week 17. Of the patients in HAVEN 3 who responded to the preference questionnaire, 89 of 95 patients (93.7%) reported preferring HEMLIBRA to their prior IV treatment, and specifically 45 of 46 patients (97.8%) preferred HEMLIBRA to their prior prophylactic FVIII treatment. In HAVEN 4, all 41 patients (100%) responded to the preference questionnaire and reported preferring HEMLIBRA to their prior IV treatment.

In HAVEN 3 and 4, the two reasons most frequently ranked by patients as the most important for their preference for HEMLIBRA were that the route of administration was easier and the frequency of treatments was lower.

Clinical Study in Pediatric Patients

HAVEN 2 (Interim Analysis)

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 thereafter.

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

HAVEN 2 Efficacy Results (Interim Analysis)

At the time of the interim analysis, efficacy was evaluated in 59 pediatric patients who were < 12 years of age and had been receiving weekly HEMLIBRA prophylaxis for at least 12 weeks, including 38 patients age 6 to < 12 years; 17 patients age 2 to < 6 years and four patients < 2 years old. Annualized bleed rate and percent of patients with zero bleeds were calculated for 59 patients (see Table 15). The median observation time for these patients was 29.6 weeks (range: 18.4 – 63).

Table 15 HAVEN 2: 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)**	**[c]Median ABR (IQR)**	**% Zero Bleeds (95% CI)**
[b]N=	**59**	**59**	**59**
Treated Bleeds	0.3 (0.1; 0.5)	0 (0; 0)	86.4 (75; 94)
All Bleeds	3.8 (2.2; 6.5)	0 (0; 3.4)	55.9 (42.4; 68.8)
Treated Spontaneous Bleeds	0 (0; 0.2)	0 (0; 0)	98.3 (90.9; 100)
Treated Joint Bleeds	0.2 (0.1; 0.4)	0 (0; 0)	89.8 (79.2; 96.2)
Treated Target Joint Bleeds	0.1 (0; 0.7)	0 (0; 0)	96.6 (88.3; 99.6)

[a]Calculated with negative binomial regression (NBR) model.
[b]Efficacy data from treated patients aged < 12 years who had been on HAVEN 2 for at least 12 weeks (n = 59), as the study aimed to primarily investigate treatment effect based on age.
[c]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 (98%) reduction in bleed rate for treated bleeds in 18 pediatric

patients who had at least 12 weeks of HEMLIBRA prophylaxis compared to their bleed rate collected in the NIS prior to enrollment (see Table 16).

Table 16 HAVEN 2: Intra-Patient Comparison of Annualized Bleed Rate (Treated Bleeds) with HEMLIBRA Prophylaxis versus Previous Bypassing Agent Prophylaxis (NIS Patients)

Endpoint	Previous treatment with bypassing agents	HEMLIBRA 1.5 mg/kg weekly
	N=18	N=18
Treated Bleeds		
ABR (95% CI)	19.8 (15.3; 25.7)	0.4 (0.15; 0.88)
% reduction (95% CI)	98% (95.7%; 99.2%)	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	77.8 (52.4; 93.6)
Median ABR (IQR)	16.2 (11.49; 25.78)	0.0 (0.00;0.00)

Confidence interval comes from negative binomial regression (NBR) model
Intra-patient comparator data from NIS
Only patients <12 years old who participated in the NIS and in HAVEN 2for 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
Note: 15 of the 18 patients received prior bypassing agent prophylaxis; 3 patients received prior episodic bypassing agents.

Pediatric Health-Related Outcomes Results

HAVEN 2 Health-Related Outcomes

In HAVEN 2, HRQoL for patients aged ≥ 8 to < 12 years was evaluated at week 25 based on the Haemo-QoL-SF questionnaire for children. The Haemo-QoL-SF is a valid and reliable measure of HRQoL (see Table 17).

Table 17 HAVEN 2: Change from Baseline to Week 25 in Haemo-QoL-SF in the Physical Health Score of Patients (≥ 8 to < 12 Years of Age) following Treatment with HEMLIBRA Prophylaxis

	Haemo-QoL-SF
Physical Health Score (range 0 to 100)[a]	
Mean baseline score (95% CI) (n = 18)	29.5 (16.4 – 42.7)
Mean change from baseline (95% CI) (n = 15)	-21.7 (-37.1 - -6.3)

[a] Lower scores (negative change scores) are reflective of better functioning.

In HAVEN 2, HRQoL for patients ages < 12 years was also evaluated at week 25 based on the Adapted InhibQoL with Aspects of Caregiver Burden questionnaire completed by caregivers. The Adapted InhibQoL is a valid and reliable measure of HRQoL (see Table 18).

Table 18 HAVEN 2: Change from Baseline to Week 25 in the Caregiver-reported Physical Health Score of Patients (< 12 Years of Age) following Treatment with HEMLIBRA Prophylaxis

	Adapted InhibQoL with Aspects of Caregiver Burden
Physical Health Score (range 0 to 100)[a]	
Mean baseline score (95% CI) (n = 54)	37.2 (31.5 – 42.8)
Mean change from baseline (95% CI) (n = 43)	-32.4 (-38.6 - -26.2)
Dealing with Inhibitor Score (range 0 to 100) [a]	
Mean baseline score (95% CI) (n = 54)	57.7 (53.3 – 62.1)
Mean change from baseline (95% CI) (n = 43)	-24.6 (-30.1 - -19.1)
Perceived Treatment Score (range 0 to 100)[a]	
Mean baseline score (95% CI) (n=54)	44.5 (40.4 – 48.6)
Mean change from baseline (95% CI) (n-43)	-16.9 (-23.1 - -10.6)
[a] Lower scores (negative change scores) are reflective of better functioning.	

Surgeries and Procedures in the HAVEN Clinical Studies

There is limited experience on bypassing agent or FVIII use during surgeries and procedures in patient receiving HEMLIBRA prophylaxis. In the clinical studies, bypassing agent or FVIII use during surgeries and procedures was determined by the investigator.

3.1.3 IMMUNOGENICITY

As with all therapeutic proteins, there is the potential for an immune response in patients treated with HEMLIBRA. Anti-drug antibodies (ADAs) were detected in a few patients participating in HEMLIBRA clinical trials, including ADAs that interfered with the activity of HEMLIBRA. The presence of ADAs may be associated with loss of efficacy. There was no clinically apparent impact of the presence of ADAs on safety.

The data reflect the number of patients whose test results were considered positive for antibodies to emicizumab using an enzyme-linked immunosorbent assay (ELISA). 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.

3.2 PHARMACOKINETIC PROPERTIES

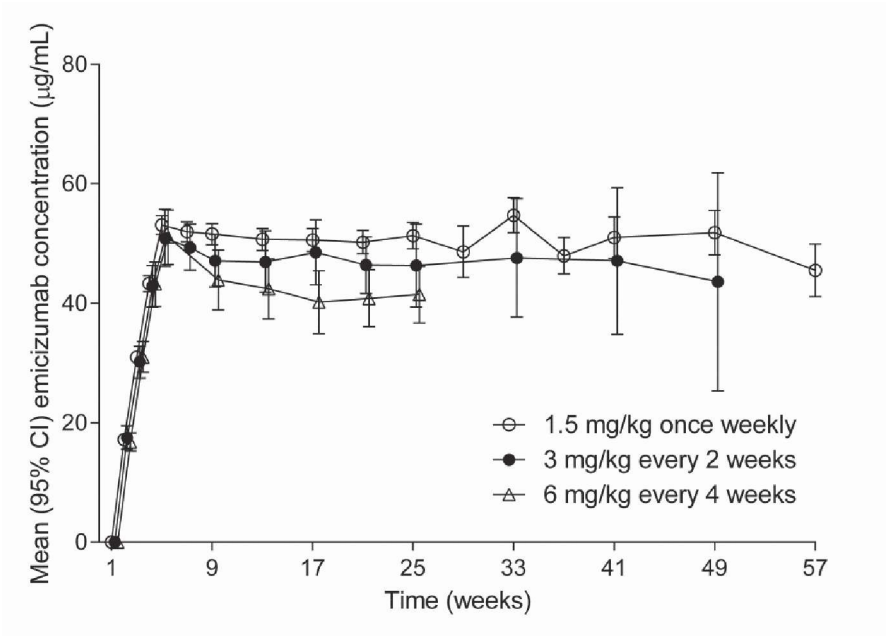
The pharmacokinetics of emicizumab were determined via a non-compartmental analysis in healthy subjects and using a population pharmacokinetic analysis on a database composed of 389 patients with hemophilia A.

3.2.1 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 (±SD) trough plasma concentrations of emicizumab achieved 52.6±13.6 µg/mL at week 5. Sustained mean trough plasma concentrations of emicizumab at steady-state were 51.2 µg/mL, 46.9 µg/mL and 38.5 µg/mL with the recommended maintenance doses of 1.5 mg/kg once weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks, respectively (Figure 1, Table 18).

Figure 1: Mean (±95%CI) Emicizumab Trough Concentrations for Maintenance Doses



The mean (±SD) C_{trough}, 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 19.

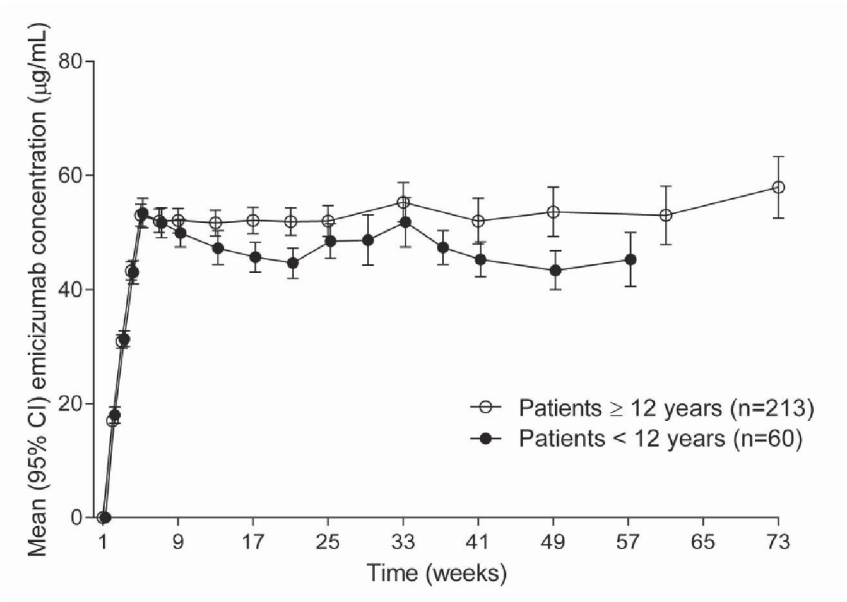
Table 19: Mean (± SD) Steady-State Emicizumab Concentrations

	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.

Similar PK profiles were 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) (see Figure 2).

Figure 2: 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)



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 section 2.2 Dosage and Administration).

3.2.2 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 section 2.2 Dosage and Administration).

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.

3.2.3 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.

3.2.4 ELIMINATION

Following intravenous administration of 0.25 mg/kg in healthy subjects, the total clearance of emicizumab was 3.26 mL/kg/day (i.e. 0.228 L/d for a 70-kg adult) and the mean terminal half-life was 26.7 days.

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 0.271 L/day and the elimination apparent half-life was 26.9 days.

Dose Linearity

Emicizumab exhibited dose-proportional pharmacokinetics in patients with hemophilia A over a dose range from 0.3 to 6 mg/kg once weekly following subcutaneous administration.

3.2.5 PHARMACOKINETICS IN SPECIAL POPULATIONS

Renal impairment

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. No dose adjustment appears to be required for patients with renal impairment.

Hepatic impairment

No dedicated studies on the effect of hepatic impairment on the pharmacokinetics of emicizumab have been conducted. 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 from 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 section 2.2.1 Special Dosage Instructions). Hepatic impairment was defined by the National Cancer Institute (NCI) criteria for hepatic dysfunction.

Pediatrics

The effect of age on the pharmacokinetics of emicizumab was assessed in a population pharmacokinetic analysis which included 5 infants (≥ 1 month to < 2 years), 55 children (≥ 2 years to < 12 years) and 50 adolescents (12 to < 18 years) with hemophilia A. Age did not affect the pharmacokinetics of emicizumab in pediatric patients (see section 2.2.1 Special Dosage Instructions).

Geriatrics

The effect of age on the pharmacokinetics of emicizumab was assessed in a population pharmacokinetic analysis which included 13 patients aged 65 years and older (no patients were older than 77 years of age). 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.

Race

Population pharmacokinetics analyses in patients with hemophilia A showed that race did not affect the pharmacokinetics of emicizumab. No dose adjustment is required for this demographic factor.

3.3 PRECLINICAL SAFETY

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.

3.3.1 CARCINOGENICITY

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

3.3.2 GENOTOXICITY

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

3.3.3 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.

3.3.4 REPRODUCTIVE TOXICITY

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

3.3.5 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.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

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

Storage condition: Store at 2°C 8°C.

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 30°C) 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.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

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 colorless to slightly yellow solution. HEMLIBRA solution should be discarded if particulate matter is visible or the product is discolored.

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

A syringe, a transfer needle (or vial adapter) 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.

Refer to the HEMLIBRA "Instructions for Use" for handling instructions when combining vials in a syringe. Do not use different HEMLIBRA vial concentrations when combining vials to administer prescribed dose.

Recommendation criteria for syringes, needles and vial adaptor 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 (in case not locally available, a syringe with Luer Slip tip can be used), graduation 0.01 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic. When used together with a vial adapter, a low dead space plunger 1 mL syringe fulfilling the above criteria must be used.

2 to 3 mL syringe
Criteria: Transparent polypropylene or polycarbonate syringe with Luer-Lock tip (in case not locally 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. When used together with a vial adapter, a low dead space plunger 3 mL syringe fulfilling the above criteria must be used.

Transfer needle or vial adapter:
Criteria for transfer needle: Stainless steel with Luer-Lock connection (in case not locally available, a needle with Luer Slip connection can be used), sterile, gauge 18 G, length 1'' to 1½'', blunted or semi-blunted tip, single-use, latex-free and non-pyrogenic.

Criteria for vial adapter: Polycarbonate with Luer-Lock connection, sterile, fitting 15 mm vial neck outer diameter, single-use, latex-free and non-pyrogenic.

Injection needle:
Criteria: Stainless steel with Luer-Lock connection (in case not locally available, an injection needle 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, vial adaptors 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, syringes and vial adaptors should never be reused.
- Place all used needles, syringes and vial adaptors 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.

5. PACKING

30 mg/ml: 30 mg in 1 ml

150 mg/ml: 60 mg in 0.4 ml

105 mg in 0.7 ml

150 mg in 1 ml

Medicine: keep out of reach of children

Current at June 2018

Imported by Roche Thailand, Ltd., Bangkok