**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use HEMLIBRA safely and effectively. See full prescribing information for HEMLIBRA.**

**HEMLIBRA® (emicizumab-kxwh) injection, for subcutaneous use**
**Initial U.S. Approval: 2017**

**WARNING: THROMBOTIC MICROANGIOPATHY and THROMBOEMBOLISM**

***See full prescribing information for complete boxed warning.***

**Cases of thrombotic microangiopathy and thrombotic events were 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. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of HEMLIBRA if symptoms occur.**

## INDICATIONS AND USAGE

HEMLIBRA is a bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. (1)

## DOSAGE AND ADMINISTRATION

Recommended loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of:

- 1.5 mg/kg once every week, or
- 3 mg/kg once every two weeks, or
- 6 mg/kg once every four weeks. (2.1)

See Full Prescribing Information for important preparation and administration instructions. (2.2)

## DOSAGE FORMS AND STRENGTHS

Injection:

- 12 mg/0.4 mL in a single-dose vial (3)
- 30 mg/mL in a single-dose vial (3)
- 60 mg/0.4 mL in a single-dose vial (3)
- 105 mg/0.7 mL in a single-dose vial (3)
- 150 mg/mL in a single-dose vial (3)
- 300 mg/2 mL (150 mg/mL) in a single-dose vial (3)

## CONTRAINDICATIONS

None (4)

## WARNINGS AND PRECAUTIONS

- Immunogenicity: Anti-emicizumab antibodies (including neutralizing antibodies) have developed in HEMLIBRA-treated patients.
- In case of clinical signs of loss of efficacy, promptly assess the etiology and consider a change in treatment if neutralizing antibodies are suspected. (5.3, 12.6, 14.3)
- Laboratory Coagulation Test Interference: HEMLIBRA interferes with activated clotting time (ACT), activated partial thromboplastin time (aPTT), and coagulation laboratory tests based on aPTT, including one-stage aPTT-based single-factor assays, aPTT-based Activated Protein C Resistance (APC-R), and Bethesda assays (clotting-based) for factor VIII (FVIII) inhibitor titers. Intrinsic pathway clotting-based laboratory tests should not be used. (5.4, 7.2)

## ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 10%) are injection site reactions, headache, and arthralgia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 07/2025**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**WARNING: THROMBOTIC MICROANGIOPATHY AND THROMBOEMBOLISM**

Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of HEMLIBRA if symptoms occur.

## 1 INDICATIONS AND USAGE

HEMLIBRA is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

**For subcutaneous use only.**

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

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

The selection of a maintenance dose should be based on healthcare provider preference with consideration of regimens that may increase patient adherence.

Discontinue the prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis.

The prophylactic use of factor VIII (FVIII) products may be continued during the first week of HEMLIBRA prophylaxis.

Missed Dose

If a dose of HEMLIBRA is missed administer as soon as possible and then resume usual dosing schedule. Do not administer two doses on the same day to make up for a missed dose.

### 2.2 Preparation and Administration

HEMLIBRA is intended for use under the guidance of a healthcare provider. After proper training in subcutaneous injection technique, a patient may self-inject, or the patient's caregiver may administer HEMLIBRA, if a healthcare provider determines that it is appropriate. Self-administration is not recommended for children less than 7 years of age. The HEMLIBRA "Instructions for Use" contains more detailed instructions on the preparation and administration of HEMLIBRA *[see Instructions for Use]*.

- Visually inspect HEMLIBRA for particulate matter and discoloration before administration. HEMLIBRA for subcutaneous administration is a colorless to slightly yellow solution. Do not use if particulate matter is visible or product is discolored.
- A syringe, a transfer needle with filter and an injection needle are needed to withdraw HEMLIBRA solution from the vial and inject it subcutaneously.
- Refer to the HEMLIBRA "Instructions for Use" for handling instructions when combining vials. Do not combine HEMLIBRA vials of different concentrations (i.e. 30 mg/mL and 150 mg/mL) in a single injection.

Please see below the selection criteria for the recommended device options:

- Administer doses of HEMLIBRA up to 1 mL with a 1 mL syringe. A 1 mL syringe fulfilling the following criteria may be used: Transparent polypropylene or polycarbonate syringe with Luer-Lock tip, graduation 0.01 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic, commercially available in the US.
- Administer doses of HEMLIBRA greater than 1 mL and up to 2 mL with a 2 mL or 3 mL syringe. A 2 mL or 3 mL syringe fulfilling the following criteria may be used: Transparent polypropylene or polycarbonate syringe with Luer-Lock tip, graduation 0.1 mL, sterile, for injection only, single-use, latex-free, and non-pyrogenic, commercially available in the US.
- A transfer needle with a filter fulfilling the following criteria should be used: Stainless steel needle with Luer-Lock connection, sterile, 18 gauge, length 1 to 1½ inch, single bevel or semi-blunted tip, single-use, latex-free, containing a 5-micron filter and non-pyrogenic, commercially available in the US.
- An injection needle fulfilling the following criteria may be used: Stainless steel with Luer-Lock connection, sterile, 26 gauge (acceptable range: 25 – 27 gauge), length preferably $^{3}/_{8}$ inch or maximal length ½ inch, single-use, latex-free and non-pyrogenic, including needle safety feature, commercially available in the US.
- Administer each injection at a different anatomic location (upper outer arms, thighs, or any quadrant of abdomen) than the previous injection. An injection should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact. Administration of HEMLIBRA in the upper outer arm should only be performed by a caregiver or healthcare provider.
- Discard any unused HEMLIBRA remaining in the single-dose vial.

## 3 DOSAGE FORMS AND STRENGTHS

HEMLIBRA is available as a colorless to slightly yellow solution in single-dose vials.

Injection:

- 12 mg/0.4 mL
- 30 mg/mL
- 60 mg/0.4 mL
- 105 mg/0.7 mL

- 150 mg/mL
- 300 mg/2 mL (150 mg/mL)

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Cases of thrombotic microangiopathy (TMA) were reported from clinical trials 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. In clinical trials, thrombotic microangiopathy was reported in 0.8% of patients (3/391) and in 8.1% of patients (3/37) who received at least one dose of aPCC. 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. One patient resumed HEMLIBRA following resolution of TMA.

Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Due to the long half-life of HEMLIBRA, the potential for an interaction with aPCC may persist for up to 6 months after the last dose. Monitor for the development of TMA when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of TMA on a case-by-case basis.

### 5.2 Thromboembolism Associated with HEMLIBRA and aPCC

Thrombotic events were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In clinical trials, thrombotic events were reported in 0.5% of patients (2/391) and in 5.4% of patients (2/37) who received at least one dose of aPCC.

No thrombotic event required anticoagulation therapy. Evidence of improvement or resolution was seen within one month following discontinuation of aPCC. One patient resumed HEMLIBRA following resolution of thrombotic event.

Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Due to the long half-life of HEMLIBRA, the potential for an interaction with aPCC may persist for up to 6 months after the last dose. Monitor for the development of thromboembolism when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms, imaging, or laboratory findings consistent with thromboembolism occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of thrombotic events on a case-by-case basis.

### 5.3 Immunogenicity

Treatment with HEMLIBRA may induce anti-drug antibodies. Anti-emicizumab-kxwh antibodies were reported in 5.1% of patients (34/668) treated with HEMLIBRA in clinical trials. Most patients with anti-emicizumab-kxwh antibodies did not experience a change in HEMLIBRA plasma concentrations or an increase in bleeding events; however, in uncommon cases (incidence < 1%), the presence of neutralizing antibodies with decreasing plasma concentration may be associated with loss of efficacy *[see Clinical Pharmacology (12.6), Clinical Studies (14.3)]*.

Monitor for clinical signs of loss of efficacy (e.g., increase in breakthrough bleeding events) and if observed, promptly assess the etiology and consider a change in treatment if neutralizing anti-emicizumab-kxwh antibodies are suspected.

### 5.4 Laboratory Coagulation Test Interference

HEMLIBRA affects intrinsic pathway clotting-based laboratory tests, including activated clotting time (ACT), activated partial thromboplastin time (aPTT), and all assays based on aPTT, such as one-stage factor VIII (FVIII) activity (Table 1). 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 FVIII inhibitor titers *[see Drug Interactions (7.2)]*. Laboratory tests affected and unaffected by HEMLIBRA are shown in Table 1.

**Table 1 Coagulation Test Results Affected and Unaffected by HEMLIBRA**

| Results Affected by HEMLIBRA | Results Unaffected by HEMLIBRA |
|---|---|
| Activated partial thromboplastin time (aPTT)<br>Bethesda assays (clotting-based) for FVIII inhibitor titers<br>One-stage, aPTT-based, single-factor assays<br>aPTT-based Activated Protein C Resistance (APC-R)<br>Activated clotting time (ACT) | Bethesda assays (bovine chromogenic) for FVIII inhibitor titers<br>Thrombin time (TT)<br>One-stage, prothrombin time (PT)-based, single-factor assays<br>Chromogenic-based single-factor assays other than FVIII*<br>Immuno-based assays (i.e., ELISA, turbidimetric methods)<br>Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210) |

*For important considerations regarding FVIII chromogenic activity assays, see *Drug Interactions (7.2)*.

# 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC *[see Warnings and Precautions (5.1)]*
- Thromboembolism Associated with HEMLIBRA and aPCC *[see Warnings and Precautions (5.2)]*

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions are based on pooled data from two randomized trials in adult and adolescent patients (HAVEN 1 and HAVEN 3), one single-arm trial in adult and adolescent patients (HAVEN 4), one single-arm trial in pediatric patients (HAVEN 2), and one dose-finding trial, in which a total of 391 male patients with hemophilia A received at least one dose of HEMLIBRA as routine prophylaxis. Two hundred eighty-one patients (72%) were adults (18 years and older), 50 (13%) were adolescents (12 years up to less than 18 years), 55 (14%) were children (2 years up to less than 12 years), and five (1%) were infants (1 month up to less than 2 years). The median duration of exposure across the studies was 34.1 weeks (0.1 to 224.4 weeks).

The most frequently reported adverse reactions observed in ≥ 10% of patients treated with HEMLIBRA were injection site reactions, headache, and arthralgia.

Four patients (1%) in the clinical trials receiving HEMLIBRA prophylaxis withdrew from treatment due to adverse reactions, which were thrombotic microangiopathy, skin necrosis and superficial thrombophlebitis, headache, and injection site reaction.

Adverse reactions observed in patients who received HEMLIBRA are shown in Table 2.

**Table 2 Adverse Reactions Reported in ≥ 5% of Patients from Pooled Clinical Trials with HEMLIBRA**

| Body System | Adverse Reaction | Number of Patients n (%) (N = 391) |
|---|---|---|
| General Disorders and Administration Site Conditions | Injection site reaction* | 85 (22%) |
| | Pyrexia | 23 (6%) |
| Nervous System Disorders | Headache | 57 (15%) |
| Gastrointestinal Disorders | Diarrhea | 22 (6%) |
| Musculoskeletal and Connective Tissue Disorders | Arthralgia | 59 (15%) |

* Includes injection site bruising, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, and injection site warmth.

*Characterization of aPCC treatment in pooled clinical trials*

There were 130 instances of aPCC treatment in 37 patients, of which 13 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 13 were associated with thrombotic events and three of the 13 were associated with TMA (Table 3). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment.

**Table 3 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 | 11 | 76 | 18 |
| 24 – 48 hours | 0 | 6 | 3[a] |
| > 48 hours | 1 | 5 | 10[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.

[a] Thrombotic event.

[b] Thrombotic microangiopathy.

*Injection Site Reactions*

In total, 85 patients (22%) reported injection site reactions (ISRs). All ISRs observed in HEMLIBRA clinical trials were reported as mild to moderate intensity and 93% resolved without treatment. The commonly reported ISR symptoms were injection site erythema (11%), injection site pain (4%), and injection site pruritus (4%).

*Other Less Common (<1%) Reactions*

- Rhabdomyolysis

Rhabdomyolysis was reported in two adult patients with asymptomatic elevations in serum creatine kinase without associated renal or musculoskeletal symptoms. In both instances, the event occurred following an increase in physical activity.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HEMLIBRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Skin and subcutaneous tissue disorders*: rash, urticaria, angioedema.

*Immune system disorders*: hypersensitivity.

## 7 DRUG INTERACTIONS

### 7.1 Hypercoagulability with Concomitant Use of aPCC

Clinical experience suggests that a drug interaction exists with HEMLIBRA and aPCC *[see Warnings and Precautions (5.1, 5.2)]*.

### 7.2 Drug-Laboratory Test Interactions

HEMLIBRA restores the tenase cofactor activity of missing activated factor VIII (FVIIIa). Coagulation laboratory tests based on intrinsic clotting (i.e., 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; 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, so it 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 Clinical Pharmacology (12.3)]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no available data on HEMLIBRA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been

conducted with emicizumab-kxwh. It is not known whether HEMLIBRA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HEMLIBRA should be used during pregnancy only if the potential benefit for the mother outweighs the risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown.

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively.

### 8.2 Lactation

Risk Summary

There is no information regarding the presence of emicizumab-kxwh in human milk, the effects on the breastfed child, or the effects on milk production.

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 child from HEMLIBRA or from the underlying maternal condition.

### 8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential should use contraception while receiving HEMLIBRA.

### 8.4 Pediatric Use

The safety and efficacy of HEMLIBRA have been established in pediatric patients. Use of HEMLIBRA in pediatric patients with hemophilia A is supported by two randomized trials (HAVEN 1 and HAVEN 3) and two single-arm trials (HAVEN 2 and HAVEN 4). All clinical trials included pediatric patients in the following age group: 47 adolescents (12 years up to less than 18 years). Only HAVEN 2 included pediatric patients in the following age groups: 55 children (2 years up to less than 12 years) and five infants (1 month up to less than 2 years). No differences in efficacy were observed between the different age groups *[see Clinical Studies (14)]*.

The steady-state plasma trough concentrations of emicizumab-kxwh were comparable in adult and pediatric patients older than 6 months at equivalent weight-based doses. Lower concentrations of emicizumab-kxwh were predicted in pediatric patients less than 6 months old *[see Clinical Pharmacology (12.3)]*.

In general, the adverse reactions in HEMLIBRA-treated pediatric patients were similar in type to those seen in adult patients with hemophilia A *[see Adverse Reactions (6.1)]*.

### 8.5 Geriatric Use

Clinical studies of HEMLIBRA did not include a sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

## 11 DESCRIPTION

Emicizumab-kxwh is a humanized monoclonal modified immunoglobulin G4 (IgG4) bispecific antibody binding factor IXa and factor X. Emicizumab-kxwh has an approximate molecular weight of 145.6 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Emicizumab-kxwh has no structural relationship or sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII.

HEMLIBRA (emicizumab-kxwh) injection is a sterile, preservative-free, colorless to slightly yellow solution for subcutaneous injection supplied in single-dose vials containing emicizumab-kxwh at 12 mg/0.4 mL, 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, 150 mg/mL, or 300 mg/2 mL.

Each single-dose 12 mg vial contains a 0.4 mL solution of emicizumab-kxwh (12 mg), L-arginine (10.5 mg), L-histidine (1.2 mg), and poloxamer 188 (0.2 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 30 mg vial contains a 1 mL solution of emicizumab-kxwh (30 mg), L-arginine (26.1 mg), L-histidine (3.1 mg), and poloxamer 188 (0.5 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 60 mg vial contains a 0.4 mL solution of emicizumab-kxwh (60 mg), L-arginine (10.5 mg), L-histidine (1.2 mg), and poloxamer 188 (0.2 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 105 mg vial contains a 0.7 mL solution of emicizumab-kxwh (105 mg), L-arginine (18.3 mg), L-histidine (2.2 mg), and poloxamer 188 (0.4 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 150 mg vial contains a 1 mL solution of emicizumab-kxwh (150 mg), L-arginine (26.1 mg), L-histidine (3.1 mg), and poloxamer 188 (0.5 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 300 mg vial contains a 2 mL solution of emicizumab-kxwh (300 mg), L-arginine (52.3 mg), L-histidine (6.2 mg), and poloxamer 188 (1 mg), adjusted to pH 6.0 with L-aspartic acid.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

HEMLIBRA bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis.

### 12.3 Pharmacokinetics

Emicizumab-kxwh exhibited dose-proportional pharmacokinetics over a dose range of 0.3 mg/kg (0.1 times approved recommended starting dosage) to 6 mg/kg following subcutaneous administration. Following multiple subcutaneous administrations of a loading dose of 3 mg/kg emicizumab-kxwh once weekly for the first 4 weeks in hemophilia A patients, mean (± SD) trough plasma concentrations of 52.6 ± 13.6 µg/mL was achieved at Week 5. Sustained mean (± SD) plasma concentrations of emicizumab-kxwh at steady-state with the recommended maintenance doses are shown in Table 4.

**Table 4 Mean (± SD) Steady-State Concentrations after emicizumab-kxwh Loading Dose by Maintenance Dose Regimen**

| | Maintenance Dose | | |
|---|---|---|---|
| **Parameters** | **1.5 mg/kg once every week** | **3 mg/kg once every two weeks** | **6 mg/kg once every four weeks** |
| $C_{max, ss}$ (µg/mL) | 55.1 ± 15.9 | 58.3 ± 16.4 | 67 ± 17.7 |
| $AUC_{ss,\tau}$ (µg/mL*day) | 376 ± 109 | 752 ± 218 | 1503 ± 437 |
| $C_{trough, ss}$ (µg/mL) | 51.2± 15.2 | 46.9 ± 14.8 | 38.5 ± 14.2 |
| $C_{max}$/ $C_{trough}$ ratio (µg/mL) | 1.08 ± 0.03 | 1.26 ± 0.12 | 1.85 ± 0.47 |

$AUC_{ss,\tau}$ = area under the concentration time curve at steady-state over the dosing interval ($\tau$ = 1, 2, or 4 weeks); $C_{max, ss}$ = maximum plasma concentration at steady state; $C_{trough, ss}$ = trough concentration at steady state.

Absorption

Following subcutaneous administration, the mean (± SD) absorption half-life was 1.6 ± 1 day.

The absolute bioavailability following subcutaneous administration of 1 mg/kg was between 80.4% and 93.1%. Similar pharmacokinetic profiles were observed following subcutaneous administration in the abdomen, upper arm, and thigh *[see Dosage and Administration (2.2)]*.

Distribution

The mean apparent volume of distribution (% coefficient of variation [%CV]) was 10.4 L (26.0%).

Elimination

The mean apparent clearance (%CV) was 0.27 L/day (28.4%) and the mean elimination apparent half-life (± SD) was 26.9 ± 9.1 days.

Specific Populations

The pharmacokinetics of emicizumab-kxwh are not influenced by age (1 year to 77 years), race (White 62.7%, Asian 22.9%, and Black 8%), inhibitor status (inhibitor present, 50%), mild hepatic impairment (defined as total bilirubin 1x to ≤1.5x the upper limit of normal (ULN) and any aspartate transaminase (AST) level), moderate hepatic impairment (defined as total bilirubin 1.5x to ≤3x the ULN and any AST level), mild renal impairment (defined as creatinine clearance (CrCl) of 60 – 89 mL/min), and moderate renal impairment (defined as CrCl of 30 – 59 mL/min). Emicizumab-kxwh has not been studied in patients with severe hepatic or renal impairment.

In pediatric patients less than 6 months old, the predicted concentrations of emicizumab-kxwh were 19% to 33% lower than the older patients, especially with the 3 mg/kg once every two weeks or 6 mg/kg once every four weeks maintenance dose.

*Body weight*: The apparent clearance and volume of distribution of emicizumab-kxwh increased with increasing body weight (9 kg to 156 kg). Dosing in mg/kg provides similar emicizumab-kxwh exposure across body weight range.

Drug Interaction Studies

No drug-drug interaction studies have been conducted with HEMLIBRA.

### 12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of HEMLIBRA or of other emicizumab products.

In the clinical trials with HEMLIBRA, 5.1% of patients (34/668) tested positive for anti-emicizumab-kxwh antibodies. Participants were exposed to emicizumab-kxwh for a median interquartile range (IQR) of 103.1 (82.4 – 148.1) weeks. Samples testing for anti-drug antibodies were obtained at baseline and at trough periodically throughout the studies duration.

Anti-Drug Antibody Effects on Pharmacokinetics

Antibody positive samples were further evaluated for neutralizing anti-emicizumab-kxwh antibodies using a modified FVIII chromogenic assay. A total of 668 patients were tested for anti-emicizumab-kxwh antibodies. 5.1% of patients (34/668) tested positive for anti-emicizumab-kxwh antibodies and 2.7% of patients (18/668) developed anti-emicizumab-kxwh antibodies that were neutralizing in vitro. Of these, 2.7% of patients (18/668), the neutralizing anti-emicizumab-kxwh antibodies did not have a clinically meaningful impact on the pharmacokinetics of HEMLIBRA in 2.1% of patients (14/668), while decreased emicizumab-kxwh plasma concentrations were observed in 0.6% of patients (4/668).

Anti-Drug Antibody Effects on Pharmacodynamics

One patient (1/668; 0.1%) developed neutralizing anti-emicizumab-kxwh antibodies and had decreased emicizumab-kxwh plasma concentrations, and experienced loss of efficacy (manifest as breakthrough bleeding) after 5 weeks of treatment and discontinued HEMLIBRA treatment. *[see Warnings and Precautions (5.3), Clinical Studies (14.3)]*.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals investigating the carcinogenic effects of emicizumab-kxwh have not been conducted. In vitro and in vivo testing of emicizumab-kxwh for genotoxicity was not conducted.

Animal fertility studies have not been conducted; however, emicizumab-kxwh 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.

## 14 CLINICAL STUDIES

### 14.1 Hemophilia A without FVIII Inhibitors

The efficacy of HEMLIBRA for routine prophylaxis in patients with hemophilia A without FVIII inhibitors was evaluated in two clinical trials [adult and adolescent studies (HAVEN 3 and HAVEN 4)].

HAVEN 3 (Adult and Adolescent Patients)

The HAVEN 3 study (NCT02847637) was a randomized, multicenter, open-label, clinical trial 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 HEMLIBRA prophylaxis, 3 mg/kg once weekly for the first 4 weeks followed by either 1.5 mg/kg once every week [Arms A and D] or 3 mg/kg once every two weeks [Arm B] thereafter, or no prophylaxis (Arm C). Patients in Arm C could switch to HEMLIBRA prophylaxis (3 mg/kg once every two weeks) after completing at least 24 weeks without prophylaxis. For Arms A and B, dose up-titration to 3 mg/kg once every week 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). For Arm D patients, dose up-titration was allowed after the second qualifying bleed. During the study, five patients underwent up-titration of their maintenance dose; however, this study was not designed to investigate the 3 mg/kg once every week dosing regimen.

Eighty-nine patients previously treated with episodic (on demand) FVIII were randomized in a 2:2:1 ratio to receive HEMLIBRA prophylaxis 1.5 mg/kg once every week (Arm A), 3 mg/kg once every two weeks (Arm B), or no prophylaxis (Arm C), 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 prophylaxis (1.5 mg/kg once every week).

Efficacy was evaluated after a minimum of 24 weeks of follow-up based on the bleed rate for bleeds requiring treatment with coagulation factors among patients previously treated with episodic (on-demand) FVIII who were randomized to HEMLIBRA prophylaxis 1.5 mg/kg once every week (Arm A) or 3 mg/kg once every two weeks (Arm B) compared with those receiving no prophylaxis (Arm C). The study also evaluated the randomized comparison of Arms A and C and Arms B and 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 compared with previous prophylactic FVIII was also evaluated in patients who had participated in a non-interventional study (NIS) prior to enrollment (Arm D). 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 3.

The efficacy results of HEMLIBRA prophylaxis (1.5 mg/kg once every week and 3 mg/kg once every two weeks) 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 5.

**Table 5 Annualized Bleed Rate with HEMLIBRA Prophylaxis versus No Prophylaxis in Patients ≥ 12 Years of Age without Factor VIII Inhibitors**

| Endpoint | HEMLIBRA 1.5 mg/kg once every week (N = 36) | HEMLIBRA 3 mg/kg once every two weeks (N = 35) | No Prophylaxis (N = 18) |
|---|---|---|---|
| **Treated Bleeds** | | | |
| ABR (95% CI) [a] | 1.5 (0.9, 2.5) | 1.3 (0.8, 2.3) | 38.2 (22.9, 63.8) |
| % reduction (95% CI)<br>p-value | 96% (92.5%, 98%)<br>< 0.0001 | 97% (93.4%, 98.3%)<br>< 0.0001 | - |
| % patients with 0 bleeds (95% CI) | 55.6 (38.1, 72.1) | 60 (42.1, 76.1) | 0 (0, 18.5) |
| Median ABR (IQR) | 0 (0, 2.5) | 0 (0, 1.9) | 40.4 (25.3, 56.7) |
| **All Bleeds** | | | |
| ABR (95% CI) [a] | 2.5 (1.6, 3.9) | 2.6 (1.6, 4.3) | 47.6 (28.5, 79.6) |
| % reduction (95% CI)<br>p-value | 95% (90.1%, 97%)<br>< 0.0001 | 94% (89.7%, 97%)<br>< 0.0001 | - |
| % patients with 0 bleeds (95% CI) | 50 (32.9, 67.1) | 40 (23.9, 57.9) | 0 (0, 18.5) |
| Median ABR (IQR) | 0.6 (0, 3.9) | 1.6 (0, 4) | 46.9 (26.1, 73.9) |
| **Treated Spontaneous Bleeds** | | | |
| ABR (95% CI) [a] | 1.0 (0.5, 1.9) | 0.3 (0.1, 0.8) | 15.6 (7.6, 31.9) |
| % reduction (95% CI)<br>p-value | 94% (84.9%, 97.5%)<br>< 0.0001 | 98% (94.4%, 99.4%)<br>< 0.0001 | - |
| % patients with 0 bleeds (95% CI) | 66.7 (49.0, 81.4) | 88.6 (73.3, 96.8) | 22.2 (6.4, 47.6) |
| Median ABR (IQR) | 0 (0, 1.3) | 0 (0, 0) | 10.8 (2.1, 26) |
| **Treated Joint Bleeds** | | | |
| ABR (95% CI) [a] | 1.1 (0.6, 1.9) | 0.9 (0.4, 1.7) | 26.5 (14.7, 47.8) |
| % reduction (95% CI)<br>p-value | 96% (91.5%, 98.1%)<br>< 0.0001 | 97% (93%, 98.5%)<br>< 0.0001 | - |
| % patients with 0 bleeds (95% CI) | 58.3 (40.8, 74.5) | 74.3 (56.7, 87.5) | 0 (0, 18.5) |
| Median ABR (IQR) | 0 (0, 1.9) | 0 (0, 1.3) | 21.3 (14.5, 41.3) |
| **Treated Target Joint Bleeds** | | | |
| ABR (95% CI) [a] | 0.6 (0.3, 1.4) | 0.7 (0.3, 1.6) | 13 (5.2, 32.3) |
| % reduction (95% CI)<br>p-value | 95% (85.7%, 98.4%)<br>< 0.0001 | 95% (85.3%, 98.2%)<br>< 0.0001 | - |
| % patients with 0 bleeds (95% CI) | 69.4 (51.9, 83.7) | 77.1 (59.9, 89.6) | 27.8 (9.7, 53.5) |
| Median ABR (IQR) | 0 (0, 1.4) | 0 (0, 0) | 12.8 (0, 39.1) |

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

[a] Based on negative binomial regression model.

In the HAVEN 3 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 Intra-Patient Comparison of Annualized Bleed Rate with HEMLIBRA Prophylaxis versus Previous FVIII Prophylaxis**

| **Endpoint** | **HEMLIBRA 1.5 mg/kg once every week (N = 48)** | **Previous FVIII Prophylaxis (N = 48)** |
|---|---|---|
| Median Observation Period (weeks) | 33.7 | 30.1 |
| **Treated Bleeds** | | |
| ABR (95% CI) [a] | 1.5 (1, 2.3) | 4.8 (3.2, 7.1) |
| % reduction (95% CI)<br>p-value | 68% (48.6%, 80.5%)<br>< 0.0001 | |
| % patients with 0 bleeds (95% CI) | 54.2 (39.2, 68.6) | 39.6 (25.8, 54.7) |
| Median ABR (IQR) | 0 (0, 2.1) | 1.8 (0, 7.6) |

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

[a] Based on negative binomial regression model.

HAVEN 4 (Adult and Adolescent Patients)

The HAVEN 4 study (NCT03020160) was a single-arm, multicenter, open-label, clinical trial 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 at 3 mg/kg once weekly for the first 4 weeks followed by 6 mg/kg once every four weeks thereafter.

Efficacy was evaluated in a subgroup of 36 patients with hemophilia A without FVIII inhibitors based on the bleed rate for bleeds requiring treatment with coagulation factors. The study also evaluated the efficacy of HEMLIBRA prophylaxis on all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

The efficacy results of HEMLIBRA prophylaxis 6 mg/kg once 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 7. The median observation time was 25.6 weeks (range 24.1 – 29.4 weeks).

**Table 7 Annualized Bleed Rate with HEMLIBRA Prophylaxis 6 mg/kg Once Every Four Weeks in Patients ≥ 12 Years of Age without Factor VIII Inhibitors**

| Endpoint | ABR[a] (95% CI) N = 36 | Median ABR (IQR) N = 36 | % Zero Bleeds (95% CI) N = 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) |

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

[a] Based on negative binomial regression model.

## 14.2 Hemophilia A with FVIII Inhibitors

The efficacy of HEMLIBRA for routine prophylaxis in patients with hemophilia A with FVIII inhibitors was evaluated in three clinical trials [adult and adolescent studies (HAVEN 1 and HAVEN 4) and a pediatric study (HAVEN 2)].

HAVEN 1 (Adult and Adolescent Patients)

The HAVEN 1 study (NCT02622321) was a randomized, multicenter, open-label, clinical trial in 109 adult and adolescent males (aged ≥ 12 years and ≥ 40 kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents. Patients received HEMLIBRA prophylaxis (Arms A, C, and D), 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once every week thereafter, or no prophylaxis (Arm B). Patients in Arm B could switch to HEMLIBRA prophylaxis after completing at least 24 weeks without prophylaxis. Dose up-titration to 3 mg/kg once every week 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; however, this study was not designed to investigate the 3 mg/kg once every week dosing regimen.

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 into 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 into Arm D to receive HEMLIBRA prophylaxis.

Efficacy was evaluated after a minimum of 24 weeks of follow-up based on the bleed rate for bleeds requiring treatment with coagulation factors among patients previously treated with

episodic bypassing agents who were randomized to HEMLIBRA prophylaxis (Arm A) compared with those receiving no prophylaxis (Arm B). The study also evaluated the randomized comparison of Arms A and B for the efficacy of HEMLIBRA prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds, as well as patient-reported symptoms and physical functioning.

The efficacy of HEMLIBRA prophylaxis compared with previous prophylactic bypassing agents was also evaluated in patients who had participated in the NIS prior to enrollment (Arm C). 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.

The efficacy results of HEMLIBRA prophylaxis 1.5 mg/kg once every week 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 8.

**Table 8 Annualized Bleed Rate with HEMLIBRA Prophylaxis versus No Prophylaxis in Patients ≥ 12 Years of Age with Factor VIII Inhibitors**

| Endpoint | HEMLIBRA 1.5 mg/kg once every week (N = 35) | No Prophylaxis (N = 18) |
|---|---|---|
| **Treated Bleeds** | | |
| ABR (95% CI) [a] | 2.9 (1.7, 5.0) | 23.3 (12.3, 43.9) |
| % reduction (95% CI) | 87% (72.3%, 94.3%) | |
| p-value | < 0.0001 | |
| % patients with 0 bleeds (95% CI) | 62.9 (44.9, 78.5) | 5.6 (0.1, 27.3) |
| Median ABR (IQR) | 0 (0, 3.7) | 18.8 (13.0, 35.1) |
| **All Bleeds** | | |
| ABR (95% CI) [a] | 5.5 (3.6, 8.6) | 28.3 (16.8, 47.8) |
| % reduction (95% CI) | 80% (62.5%, 89.8%) | |
| p-value | < 0.0001 | |
| % patients with 0 bleeds (95% CI) | 37.1 (21.5, 55.1) | 5.6 (0.1, 27.3) |
| Median ABR (IQR) | 2 (0, 9.9) | 30.2 (18.3, 39.4) |
| **Treated Spontaneous Bleeds** | | |
| ABR (95% CI) [a] | 1.3 (0.7, 2.2) | 16.8 (9.9, 28.3) |
| % reduction (95% CI) | 92% (84.6%, 96.3%) | |
| p-value | < 0.0001 | |
| % patients with 0 bleeds (95% CI) | 68.6 (50.7, 83.1) | 11.1 (1.4, 34.7) |
| Median ABR (IQR) | 0 (0, 3.3) | 15.2 (6.6, 30.4) |
| **Treated Joint Bleeds** | | |
| ABR (95% CI) [a] | 0.8 (0.3, 2.2) | 6.7 (2.0, 22.4) |

| | | |
|---|---|---|
| % reduction (95% CI)<br>p-value | 89% (48%, 97.5%)<br>0.0050 | |
| % patients with 0 bleeds (95% CI) | 85.7 (69.7, 95.2) | 50.0 (26.0, 74.0) |
| Median ABR (IQR) | 0 (0, 0) | 1 (0, 14.4) |
| **Treated Target Joint Bleeds** | | |
| ABR (95% CI) [a] | 0.1 (0.03, 0.6) | 3.0 (1.0, 9.1) |
| % reduction (95% CI)<br>p-value | 95% (77.3%, 99.1%)<br>0.0002 | |
| % patients with 0 bleeds (95% CI) | 94.3 (80.8, 99.3) | 50.0 (26.0, 74.0) |
| Median ABR (IQR) | 0 (0, 0) | 1 (0, 6.5) |

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

[a] Based on negative binomial regression model.

Descriptive analyses were conducted to assess HEMLIBRA prophylaxis once every week using 12-week treatment intervals up to Week 72. The descriptive mean ABRs for treated bleeds are shown in Table 9.

**Table 9 Annualized Bleed Rate with HEMLIBRA Prophylaxis Once Every Week per 12-Week Intervals in Patients ≥ 12 Years of Age with Factor VIII Inhibitors**

| **Endpoint** | **Time Interval (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 (0.3, 7.6) | 0.9 (0, 5.5) | 0.4 (0, 4.4) | 0.5 (0, 4.7) | 0.6 (0, 4.9) |

ABR = annualized bleed rate; CI = confidence interval based on Poisson distribution; N = number of patients who contributed data for analyses at each time interval.

In the HAVEN 1 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 (Table 10).

**Table 10 Intra-Patient Comparison of Annualized Bleed Rate with HEMLIBRA Prophylaxis versus Previous Bypassing Agent Prophylaxis**

| **Endpoint** | **HEMLIBRA 1.5 mg/kg once every week (N = 24)** | **Previous Bypassing Agent Prophylaxis (N = 24)** |
|---|---|---|
| Median Observation Period (weeks) | 30.1 | 32.1 |
| **Treated Bleeds** | | |
| ABR (95% CI) [a] | 3.3 (1.3, 8.1) | 15.7 (11.1, 22.3) |

| | | |
|---|---|---|
| % reduction (95% CI)<br>p-value | 79% (51.4%, 91.1%)<br>0.0003 | |
| % patients with 0 bleeds (95% CI) | 70.8 (48.9, 87.4) | 12.5 (2.7, 32.4) |
| Median ABR (IQR) | 0 (0, 2.2) | 12 (5.7, 24.2) |

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

[a] Based on negative binomial regression model.

The HAVEN 1 study evaluated patient-reported hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement and difficulty walking far) using the Physical Health Score of the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire for patients ≥ 18 years of age. The HEMLIBRA prophylaxis arm (Arm A) showed an improvement compared with the no prophylaxis arm (Arm B) in the Haem-A-QoL Physical Health Subscale score at the Week 25 assessment (Table 11). The improvement in the Physical Health Score was further supported by the Total Score as measured by the Haem-A-QoL at Week 25.

**Table 11 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 Week 25**

| **Haem-A-QoL Scores at Week 25** | **HEMLIBRA 1.5 mg/kg once every week (N = 25[a])** | **No Prophylaxis (N = 14[a])** |
|---|---|---|
| **Physical Health Score (range 0 to 100)[b]** | | |
| Adjusted mean [c] | 32.6 | 54.2 |
| Difference in adjusted means (95% CI) | 21.6 (7.9, 35.2) | |
| p-value | 0.0029 | |

[a] Number of patients ≥ 18 years who completed the Haem-A-QoL questionnaire.

[b] Lower scores are reflective of better functioning.

[c] Adjusted for baseline, and baseline by treatment group interaction.

HAVEN 2 (Pediatric Patients)

The HAVEN 2 study (NCT02795767) was a single-arm, multicenter, open-label, clinical trial in pediatric males (age < 12 years, or 12 – 17 years who weigh < 40 kg) with hemophilia A with FVIII inhibitors. Patients received HEMLIBRA prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once every week thereafter.

The study evaluated the efficacy of HEMLIBRA prophylaxis, including the efficacy of HEMLIBRA prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agent treatment in patients who had participated in a non-interventional study (NIS) prior to enrollment (intra-patient 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 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 age < 2 years.

Annualized bleed rate (ABR) and percent of patients with zero bleeds were calculated for 59 patients (Table 12). The median observation time for these patients was 29.6 weeks (range 18.4 – 63 weeks).

**Table 12 Annualized Bleed Rate with HEMLIBRA Prophylaxis 1.5 mg/kg Once Every Week in Pediatric Patients < 12 Years of Age with Factor VIII Inhibitors (Interim Analysis)**

| Endpoint | ABR[a] (95% CI) N = 59 | Median ABR (IQR) N = 59 | % Zero Bleeds (95% CI) N = 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) |

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile.
[a] Based on negative binomial regression model.

In the intra-patient analysis, 18 pediatric patients who had participated in the NIS had an ABR for treated bleeds of 19.8 (95% CI [15.3, 25.7]) on previous bypassing agent treatment (prophylactic treatment in 15 patients and on-demand treatment for 3 patients). HEMLIBRA prophylaxis resulted in an ABR for treated bleeds of 0.4 (95% CI [0.2, 0.9]) based on negative binomial regression, corresponding to a 98% reduction in bleed rate. On HEMLIBRA prophylaxis, 14 patients (77.8%) had zero treated bleeds.

The HAVEN 2 study evaluated patient-reported hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement) using the Physical Health Score of the Hemophilia-specific Quality of Life Short Form (Haemo-QoL-SF) questionnaire for patients ≥ 8 to < 12 years of age. HEMLIBRA prophylaxis showed improvement from baseline in the Haemo-QoL-SF Physical Health Subscale score at the Week 25 assessment.

HAVEN 4 (Adult and Adolescent Patients)

The HAVEN 4 study (NCT03020160) was a single-arm, multicenter, open-label, clinical trial 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 at 3 mg/kg once weekly for the first 4 weeks followed by 6 mg/kg once every four weeks thereafter.

Efficacy was evaluated in a subgroup of 5 patients with hemophilia A 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, 4 patients had zero treated bleeds.

The efficacy results of HEMLIBRA prophylaxis (1.5 mg/kg once every week, 3 mg/kg once every two weeks, and 6 mg/kg once every four weeks) with respect to rate of treated bleeds are shown in Table 13.

**Table 13 Annualized Bleed Rate (Treated Bleeds) with HEMLIBRA Prophylaxis in Patients with or without Factor VIII Inhibitors**

| Endpoint | HAVEN 1 | | HAVEN 2 | HAVEN 3 | | | HAVEN 4 |
|---|---|---|---|---|---|---|---|
| | HEMLIBRA 1.5 mg/kg once every week (N = 35) | No Prophylaxis (N = 18) | HEMLIBRA 1.5 mg/kg once every week (N = 59) | HEMLIBRA 1.5 mg/kg once every week (N = 36) | HEMLIBRA 3 mg/kg once every two weeks (N = 35) | No Prophylaxis (N = 18) | HEMLIBRA 6 mg/kg once every four weeks (N = 41) |
| Median Efficacy Period (weeks) | 29.3 | 24 | 29.6 | 29.6 | 31.3 | 24 | 25.6 |
| ABR (95% CI) [a] | 2.9 (1.7, 5) | 23.3 (12.3, 43.9) | 0.3 (0.1, 0.5) | 1.5 (0.9, 2.5) | 1.3 (0.8, 2.3) | 38.2 (22.9, 63.8) | 2.4 (1.4, 4.3) |
| % reduction vs no prophylaxis (95% CI), p-value | 87% (72.3%, 94.3%) < 0.0001 | - | - | 96% (92.5%, 98%) < 0.0001 | 97% (93.4%, 98.3%) < 0.0001 | - | - |
| % patients with 0 bleeds (95% CI) | 62.9 (44.9, 78.5) | 5.6 (0.1, 27.3) | 86.4 (75, 94) | 55.6 (38.1, 72.1) | 60 (42.1, 76.1) | 0 (0, 18.5) | 56.1 (39.7, 71.5) |
| % patients with 0 - 3 bleeds (95% CI) | 85.7 (69.7, 95.2) | 11.1 (1.4, 34.7) | 100 (93.9, 100) | 91.7 (77.5, 98.2) | 94.3 (80.8, 99.3) | 5.6 (0.1, 27.3) | 90.2 (76.9, 97.3) |
| Median ABR (IQR) | 0 (0, 3.7) | 18.8 (13, 35.1) | 0 (0, 0) | 0 (0, 2.5) | 0 (0, 1.9) | 40.4 (25.3, 56.7) | 0 (0, 2.1) |

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile; HAVEN 1 = adult and adolescent patients with factor VIII inhibitors; HAVEN 2 = pediatric patients with factor VIII inhibitors; HAVEN 3 = adult and adolescent patients without factor VIII inhibitors; HAVEN 4 = adult and adolescent patients with or without factor VIII inhibitors.

[a] Based on negative binomial regression model.

### 14.3 Clinical Impact of Immunogenicity

One patient (1/668, 0.1%) with neutralizing anti-emicizumab-kxwh antibodies in the HEMLIBRA clinical trials had decreased emicizumab-kxwh plasma concentrations and loss of efficacy (manifest as breakthrough bleeding) after 5 weeks of treatment and discontinued HEMLIBRA treatment *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.6)]*.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HEMLIBRA (emicizumab-kxwh) injection is available as a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials in the following dosage strengths:

| Strength | Nominal Volume | Concentration | Package Size (per carton) | Cap Color | NDC |
|---|---|---|---|---|---|
| 12 mg | 0.4 mL | 30 mg/mL | 1 vial | Grey | 50242-927-01 |
| 30 mg | 1 mL | 30 mg/mL | 1 vial | Sky Blue | 50242-920-01 |
| 60 mg | 0.4 mL | 150 mg/mL | 1 vial | Purple | 50242-921-01 |
| 105 mg | 0.7 mL | 150 mg/mL | 1 vial | Turquoise | 50242-922-01 |
| 150 mg | 1 mL | 150 mg/mL | 1 vial | Brown | 50242-923-01 |
| 300 mg | 2 mL | 150 mg/mL | 1 vial | Yellow | 50242-930-01 |

Storage and Handling

- Store HEMLIBRA vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.
- Prior to administration, if needed, unopened vials of HEMLIBRA may be stored out of and then returned to refrigeration. The temperature and total combined time out of refrigeration should not exceed 30°C (86°F) and 7 days (at a temperature below 30°C [86°F]), respectively.
- Once removed from the vial, discard HEMLIBRA if not used immediately.
- Discard any unused HEMLIBRA.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Use of Bypassing Agents or FVIII

Inform the patient and/or caregiver that HEMLIBRA increases coagulation potential. Advise the patient and/or caregiver to discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Advise the patient and/or caregiver that prophylactic use of FVIII may be continued for the first week of HEMLIBRA prophylaxis. Discuss the appropriate

dosing of concomitant agents such as bypassing agents or FVIII with the patient and/or caregiver prior to starting HEMLIBRA prophylaxis *[see Warnings and Precautions (5.1, 5.2) and Drug Interactions (7.1)]*.

Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Inform the patient and/or caregiver of the potential risk of thrombotic microangiopathy if aPCC is administered while receiving HEMLIBRA prophylaxis. Instruct the patient and/or caregiver to consult their healthcare provider if aPCC is required in cumulative doses exceeding 100 U/kg. Advise the patient and/or caregiver to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur *[see Warnings and Precautions (5.1)]*.

Thromboembolism Associated with HEMLIBRA and aPCC

Inform the patient and/or caregiver of the potential risk of thromboembolism if aPCC is administered while receiving HEMLIBRA prophylaxis. Instruct the patient and/or caregiver to consult their healthcare provider if aPCC is required in cumulative doses exceeding 100 U/kg. Advise the patient and/or caregiver to seek immediate medical attention if any signs or symptoms of thromboembolism occur *[see Warnings and Precautions (5.2)]*.

Immunogenicity

Inform the patient and/or caregiver of the uncommon occurrence (incidence < 1%) of loss of efficacy while receiving HEMLIBRA prophylaxis due to immunogenicity (neutralizing anti-emicizumab-kxwh antibodies). Instruct the patient and/or caregiver to promptly report clinical signs of loss of efficacy (e.g., increase in breakthrough bleeding events) *[see Warnings and Precautions (5.3)]*.

Laboratory Coagulation Test Interference

Inform the patient and/or caregiver that HEMLIBRA interferes with some laboratory tests that measure blood clotting and may cause a false reading. Advise the patient and/or caregiver that they should notify any healthcare provider about this possibility prior to any blood tests or medical procedures *[see Warnings and Precautions (5.4)]*.

Instruction on Injection Technique

HEMLIBRA is intended for use under the guidance of a healthcare provider. If a patient or caregiver is to administer subcutaneous HEMLIBRA, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous HEMLIBRA and the suitability for home use *[see Instructions for Use]*.

Advise the patient to follow the recommendations in the FDA-approved patient labeling regarding proper sharps disposal.

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Manufactured by:
**Genentech, Inc**.
A Member of the Roche Group
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**Medication Guide**

**HEMLIBRA® (hem-lee-bruh)**

**(emicizumab-kxwh)**

**injection, for subcutaneous use**

**What is the most important information I should know about HEMLIBRA?**

**HEMLIBRA increases the potential for your blood to clot. Carefully follow your healthcare provider's instructions regarding when to use an on-demand bypassing agent or factor VIII (FVIII) and the recommended dose and schedule to use for breakthrough bleed treatment.**

**HEMLIBRA may cause the following serious side effects when used with activated prothrombin complex concentrate (aPCC; FEIBA®), including:**

- **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. Get medical help right away if you have any of the following signs or symptoms during or after treatment with HEMLIBRA:
  - confusion
  - weakness
  - swelling of arms and legs
  - yellowing of skin and eyes
  - stomach (abdomen) or back pain
  - nausea or vomiting
  - feeling sick
  - decreased urination
- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in your arm, leg, lung, or head. Get medical help right away if you have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:
  - swelling in arms or legs
  - pain or redness in your arms or legs
  - shortness of breath
  - chest pain or tightness
  - fast heart rate
  - cough up blood
  - feel faint
  - headache
  - numbness in your face
  - eye pain or swelling
  - trouble seeing

**If aPCC (FEIBA®) is needed, talk to your healthcare provider in case you feel you need more than 100 U/kg of aPCC (FEIBA®) total.**

**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).**

See **"What are the possible side effects of HEMLIBRA?"** for more information about side effects.

**What is HEMLIBRA?**

HEMLIBRA is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children, ages newborn and older, with hemophilia A with or without factor VIII inhibitors.

Hemophilia A is a bleeding condition people can be born with where a missing or faulty blood clotting factor (factor VIII) prevents blood from clotting normally.

HEMLIBRA is a therapeutic antibody that bridges clotting factors to help your blood clot.

**Before using HEMLIBRA, tell your healthcare provider about all of your medical conditions, including if you:**

- are pregnant or plan to become pregnant. It is not known if HEMLIBRA may harm your unborn baby. Females who are able to become pregnant should use birth control (contraception) during treatment with HEMLIBRA.
- are breastfeeding or plan to breastfeed. It is not known if HEMLIBRA passes into your breast milk.

**Tell your healthcare provider about all the medicines you take**, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

**How should I use HEMLIBRA?**

**See the detailed "Instructions for Use" that comes with your HEMLIBRA for information on how to prepare and inject a dose of HEMLIBRA, and how to properly throw away (dispose of) used needles and syringes.**

- Use HEMLIBRA exactly as prescribed by your healthcare provider.
- **Stop (discontinue) prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis.**
- **You may continue prophylactic use of FVIII for the first week of HEMLIBRA prophylaxis.**
- HEMLIBRA is given as an injection under your skin (subcutaneous injection) by you or a caregiver.
- Your healthcare provider should show you or your caregiver how to prepare, measure, and inject your dose of HEMLIBRA before you inject yourself for the first time.
- Do not attempt to inject yourself or another person unless you have been taught how to do so by a healthcare provider.
- Your healthcare provider will prescribe your dose based on your weight. If your weight changes, tell your healthcare provider.
- You will receive HEMLIBRA 1 time a week for the first four weeks. Then you will receive a maintenance dose as prescribed by your healthcare provider.
- If you miss a dose of HEMLIBRA on your scheduled day, you should give the dose as soon as you remember. You must give the missed dose as soon as possible before the next scheduled dose, and then continue with your normal dosing schedule. **Do not** give two doses on the same day to make up for a missed dose.
- HEMLIBRA may interfere with laboratory tests that measure how well your blood is clotting and may cause a false reading. Talk to your healthcare provider about how this may affect your care.

**What are the possible side effects of HEMLIBRA?**

- See "**What is the most important information I should know about HEMLIBRA?"**

**The most common side effects of HEMLIBRA include:**

- redness, tenderness, warmth, or itching at the site of injection
- headache
- joint pain

These are not all of the possible side effects of HEMLIBRA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store HEMLIBRA?**

- Store HEMLIBRA in the refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- Store HEMLIBRA in the original carton to protect the vials from light.
- Do not shake HEMLIBRA.
- If needed, unopened vials of HEMLIBRA can be stored out of the refrigerator and then returned to the refrigerator. HEMLIBRA should not be stored out of the refrigerator for more than a total of 7 days or at a temperature greater than 86°F (30°C).
- After HEMLIBRA is transferred from the vial to the syringe, HEMLIBRA should be used right away.
- Throw away (dispose of) any unused HEMLIBRA left in the vial.

**Keep HEMLIBRA and all medicines out of the reach of children.**

**General information about the safe and effective use of HEMLIBRA.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HEMLIBRA for a condition for which it was not prescribed. Do not give HEMLIBRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about HEMLIBRA that is written for health professionals.

**What are the ingredients in HEMLIBRA?**

**Active ingredient:** emicizumab-kxwh

**Inactive ingredients:** L-arginine, L-histidine, poloxamer 188, and L-aspartic acid.

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For more information, go to www.HEMLIBRA.com or call 1-866-HEMLIBRA.