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 with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. (1)

DOSAGE AND ADMINISTRATION

Recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly. (2.1)

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

DOSAGE FORMS AND STRENGTHS

Injection:
- 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)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- 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. (5.3, 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 FDA-approved patient labeling.

Revised: 11/2017

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 with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

For subcutaneous use only.

The recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly.

Missed Dose

If a dose of HEMLIBRA is not administered on the scheduled day, administer as soon as possible before the day of the next scheduled dose, and then resume usual weekly dosing schedule. Do not double doses 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 aged less than 7 years old. 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, 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 use different HEMLIBRA vials of different concentrations when combining vials to administer prescribed dose.
- 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-Lok™ 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-Lok™ tip, graduation 0.1 mL, sterile, for injection only, single-use, latex-free, and non-pyrogenic, commercially available in the US.

- A transfer needle fulfilling the following criteria may be used: Stainless steel needle with Luer-Lok™ connection, sterile, 18 gauge, length 1½ inch, semi-blunted tip, single-use, latex-free, and non-pyrogenic, commercially available in the US.
- An injection needle fulfilling the following criteria may be used: Stainless steel with Luer-Lok™ connection, sterile, 26 gauge, 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:

- 30 mg/mL
- 60 mg/0.4 mL
- 105 mg/0.7 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 1.6% of patients (3/189) and in 8.3% of patients (3/36) 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. 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 1.1% of patients (2/189) and in 5.6% of patients (2/36) 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. 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 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) Bethesda assays (clotting-based) for FVIII inhibitor titers One-stage, aPTT-based, single-factor assays 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 (i.e., ELISA, turbidimetric methods) Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)

*For important considerations regarding FVIII chromogenic activity assays, see *Drug 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 a randomized trial (HAVEN 1), single-arm trial (HAVEN 2), and a dose-finding trial, in which a total of 189 male patients with hemophilia A received at least one dose of HEMLIBRA as routine prophylaxis. Ninety-four patients (50%) were adults (18 years and older), 38 (20%) were adolescents (12 years up to less than 18 years), 55 (29%) were children (2 years up to less than 12 years), and two (1%) were infants (1 month up to less than 2 years). Seven of the 189 patients (4%) included in the safety

population were patients without FVIII inhibitors from the dose-finding trial. The median duration of exposure across the studies was 38 weeks (0.8 to 177.2 weeks).

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

Four patients (2.1%) in the clinical trials receiving HEMLIBRA prophylaxis withdrew from treatment due to adverse reactions, which were thrombotic microangiopathy, skin necrosis and superficial thrombophlebitis, 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 = 189)
General Disorders and Administration Site Conditions	Injection site reaction*	35 (19%)
	Pyrexia	13 (7%)
Nervous System Disorders	Headache	28 (15%)
Gastrointestinal Disorders	Diarrhea	12 (6%)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	18 (10%)
	Myalgia	9 (5%)

* 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 urticarial, and injection site warmth.

Characterization of aPCC treatment in pooled clinical trials

There were 125 instances of aPCC treatment in 36 patients, of which 13 instances (10.4%) 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	7	76	18
24 – 48 hours	0	6	3[b]
> 48 hours	1	4	10[a,a,a,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 microangiopathy

[b] Thrombotic event

Injection Site Reactions

In total, 35 patients (19%) reported injection site reactions (ISRs). All ISRs observed in HEMLIBRA clinical trials were reported as mild to moderate intensity and 88% resolved

without treatment. The commonly reported ISR symptoms were injection site erythema (7.4%), injection site pruritus (5.3%), and injection site pain (5.3%).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to emicizumab-kxwh in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of HEMLIBRA was evaluated using an enzyme-linked immunosorbent assay (ELISA) or an electrochemiluminescence (ECL) assay. No patients tested positive for anti-emicizumab antibodies in HAVEN 1 and HAVEN 2 (n = 171). Four patients tested positive for anti-emicizumab antibodies in the dose-finding trial (n = 18). The anti-emicizumab antibody positive rate may be under-reported due to the limitation of the assay.

7 DRUG INTERACTIONS

7.1 Hypercoagulability with Concomitant Use of aPCC, rFVIIa, or FVIII

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

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

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 with FVIII inhibitors is supported by a randomized trial (HAVEN 1) and a single-arm trial (HAVEN 2). HAVEN 1 included pediatric patients in the following age group: 38 adolescents (12 years to less than 18 years). HAVEN 2 included pediatric patients in the following age groups: 55 children (2 years up to less than 12 years) and two infants (1 month up to less than 2 years). No differences in efficacy were observed between the different age groups *[see Clinical Studies (14)]*.

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

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

8.5 Geriatric Use

Clinical studies of HEMLIBRA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Emicizumab-kxwh is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure 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 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, or 150 mg/mL.

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.

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 3 mg/kg once weekly following subcutaneous administration. 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-kxwh increased to achieve 54.6 ± 14.3 µg/mL at Week 5. Trough plasma concentrations above 50 µg/mL were sustained thereafter with the recommended weekly dosage of 1.5 mg/kg; the mean (± SD) trough plasma concentrations of emicizumab-kxwh at steady-state was 52.8 ± 13.5 µg/mL.

Absorption

Following subcutaneous administration, the mean (± SD) absorption half-life was 1.7 ± 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 was 11.4 L (95% confidence interval (CI) [10.6, 12.1]).

Elimination

The mean apparent clearance (95% CI) was 0.24 L/day (0.22, 0.26) and the mean elimination apparent half-life (± SD) was 27.8 ± 8.1 days.

Specific Populations

The pharmacokinetics of emicizumab-kxwh are not influenced by age (3 years to 75 years), race (White 54%, Asian 30.5% and Black 8.5%), inhibitor status (inhibitor present, 92%), mild

hepatic impairment (defined as total bilirubin 1x to ≤ 1.5x the upper limit of normal (ULN) and any aspartate transaminase (AST) level) and moderate hepatic impairment (defined as total bilirubin 1.5x to ≤ 3x the ULN and any AST level).

Body weight: The apparent clearance and volume of distribution of emicizumab-kxwh increased with increasing body weight (14.2 kg to 131 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.

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

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

HAVEN 1

The HAVEN 1 study (NCT02622321) was a randomized, multicenter, open-label, clinical trial in 109 adult and adolescent males (aged 12 to 75 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 weekly HEMLIBRA prophylaxis (Arms A, C, and D), 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter, or no prophylaxis (Arm B). Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on HEMLIBRA prophylaxis in case of suboptimal efficacy (i.e., ≥ 2 spontaneous and clinically significant bleeds). 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). Patients randomized to Arm B could switch to HEMLIBRA prophylaxis after completing at least 24 weeks without prophylaxis.

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled into Arm C to receive HEMLIBRA prophylaxis. Seven patients previously treated with episodic (on-demand) bypassing agents who had participated in a non-interventional study (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 based on the annualized bleeding rate (ABR) requiring treatment with coagulation factors (minimum of 24 weeks or date of discontinuation) 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 trial also evaluated the randomized comparison of Arms A and B for the efficacy of weekly 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 study also evaluated the efficacy of weekly HEMLIBRA prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agents in patients who had participated in the NIS prior to enrollment (Arms A and C, respectively). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity in both periods.

The efficacy results of HEMLIBRA prophylaxis compared with no prophylaxis in bleed rate for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds are shown in Table 4.

Table 4 Annualized Bleed Rate with HEMLIBRA Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age

Endpoint	HEMLIBRA Prophylaxis (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) p-value	87% (72.3%, 94.3%) < 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) p-value	80% (62.5%, 89.8%) < 0.0001	
% patients with 0 bleeds (95% CI)	37.1 (21.5, 55.1)	5.6 (0.1, 27.3)
Treated Spontaneous Bleeds		
ABR (95% CI) [a]	1.3 (0.7, 2.2)	16.8 (9.9, 28.3)
% reduction (95% CI) p-value	92% (84.6%, 96.3%) < 0.0001	
% patients with 0 bleeds (95% CI)	68.6 (50.7, 83.1)	11.1 (1.4, 34.7)
Treated Joint Bleeds		
ABR (95% CI) [a]	0.8 (0.3, 2.2)	6.7 (2.0, 22.4)
% reduction (95% CI) p-value	89% (48%, 97.5%) 0.0050	
% patients with 0 bleeds (95% CI)	85.7 (69.7, 95.2)	50.0 (26.0, 74.0)
Treated Target Joint Bleeds		
ABR (95% CI) [a]	0.1 (0.03, 0.6)	3.0 (1.0, 9.1)
% reduction (95% CI) p-value	95% (77.3%, 99.1%) 0.0002	
% patients with 0 bleeds (95% CI)	94.3 (80.8, 99.3)	50.0 (26.0, 74.0)

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

[a] Based on negative binomial regression.

In the 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 5).

Table 5 Intra-Patient Comparison of Annualized Bleed Rate with HEMLIBRA Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	HEMLIBRA Prophylaxis (N = 24)	Previous Bypassing Agent Prophylaxis (N = 24)
Treated Bleeds		
ABR (95% CI) [a]	3.3 (1.3, 8.1)	15.7 (11.1, 22.3)
% reduction (95% CI) p-value	79% (51.4%, 91.1%) 0.0003	
% patients with zero 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.

The 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 aged ≥ 18 years. The weekly 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 6). 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 6 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	HEMLIBRA Prophylaxis (N=25[a])	No Prophylaxis (N=14[a])
Physical Health Score (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

The HAVEN 2 study (NCT02795767) was a single-arm, multicenter, open-label, clinical study 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 weekly thereafter.

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

At the time of the interim analysis, efficacy was evaluated in 23 pediatric patients who were < 12 years old and had been receiving weekly HEMLIBRA prophylaxis for at least 12 weeks, including 19 patients age 6 to < 12 years and 4 patients age 2 to < 6 years.

Annualized bleed rate (ABR) and percent of patients with zero bleeds were calculated for 23 patients (Table 7). The median observation time for these patients was 38.1 weeks (12.7 – 41.6 weeks).

Table 7 Annualized Bleed Rate with HEMLIBRA Prophylaxis in Pediatric Patients < 12 Years of Age (Interim Analysis)

Endpoint	ABR[a] (95% CI) N = 23	Median ABR (IQR) N = 23	% Zero Bleeds (95% CI) N = 23
Treated Bleeds	0.2 (0.1, 0.6)	0 (0, 0)	87 (66.4, 97.2)
All Bleeds	2.9 (1.8, 4.9)	1.5 (0, 4.5)	34.8 (16.4, 57.3)
Treated Spontaneous Bleeds	0.1 (0, 0.5)	0 (0, 0)	95.7 (78.1, 99.9)
Treated Joint Bleeds	0.1 (0, 0.5)	0 (0, 0)	95.7 (78.1, 99.9)
Treated Target Joint Bleeds	Not Estimable*	0 (0, 0)	100 (85.2, 100)

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

* No treated target joint bleeds reported

[a] Based on negative binomial regression

In the intra-patient analysis, 13 pediatric patients who had participated in the NIS had an ABR of 17.2 (95% CI [12.4, 23.8]) on previous bypassing agent treatment (prophylactic treatment in 12 patients and on-demand treatment for one patient). Weekly HEMLIBRA prophylaxis resulted in an ABR for treated bleeds of 0.2 (95% CI [0.1, 0.8]) based on negative binomial regression, corresponding to a 99% reduction in bleed rate. On HEMLIBRA prophylaxis, 11 patients (84.6%) had zero treated bleeds.

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
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

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 (Patient Information and Instructions for Use).

Use of Bypassing Agents

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. Discuss the use of bypassing agents with the patient and/or caregiver prior to starting HEMLIBRA prophylaxis *[see Adverse Reactions (6.1)]*.

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)]*.

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 (5.3)]*.

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.

HEMLIBRA® [emicizumab-kxwh]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No. 1048

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. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow your healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule you should use.

HEMLIBRA may cause the following serious side effects when used with 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.

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 with hemophilia A with 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.
- 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.
- 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 before the next scheduled dosing day and then continue with your normal weekly dosing schedule. Do not double your dose 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 7 days at 86°F (30°C) or below.
- 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

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

Manufactured by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990
U.S. License No. 1048

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

 This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 11/2017