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RESEARCH**

APPLICATION NUMBER:

761083Orig1s000

LABELING

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 $\geq 10\%$) 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

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: THROMBOTIC MICROANGIOPATHY AND THROMBOEMBOLISM**

3 Cases of thrombotic microangiopathy and thrombotic events were reported when on average
4 a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate
5 was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis.

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

8 **1 INDICATIONS AND USAGE**

9 HEMLIBRA is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding
10 episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency)
11 with factor VIII inhibitors.

12 **2 DOSAGE AND ADMINISTRATION**

13 **2.1 Recommended Dosage**

14 **For subcutaneous use only.**

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

17 Missed Dose

18 If a dose of HEMLIBRA is not administered on the scheduled day, administer as soon as
19 possible before the day of the next scheduled dose, and then resume usual weekly dosing
20 schedule. Do not double doses to make up for a missed dose.

21 **2.2 Preparation and Administration**

22 HEMLIBRA is intended for use under the guidance of a healthcare provider. After proper
23 training in subcutaneous injection technique, a patient may self-inject, or the patient's caregiver
24 may administer HEMLIBRA, if a healthcare provider determines that it is appropriate.

25 Self-administration is not recommended for children aged less than 7 years old. The HEMLIBRA
26 "Instructions for Use" contains more detailed instructions on the preparation and administration
27 of HEMLIBRA [*see Instructions for Use*].

- 28 • Visually inspect HEMLIBRA for particulate matter and discoloration before administration.
29 HEMLIBRA for subcutaneous administration is a colorless to slightly yellow solution. Do not
30 use if particulate matter is visible or product is discolored.
- 31 • A syringe, a transfer needle, and an injection needle are needed to withdraw HEMLIBRA
32 solution from the vial and inject it subcutaneously.
- 33 • Refer to the HEMLIBRA "Instructions for Use" for handling instructions when combining
34 vials. Do not use different HEMLIBRA vials of different concentrations when combining
35 vials to administer prescribed dose.
- 36 • Administer doses of HEMLIBRA up to 1 mL with a 1 mL syringe. A 1 mL syringe fulfilling
37 the following criteria may be used: Transparent polypropylene or polycarbonate syringe with
38 Luer-Lok™ tip, graduation 0.01 mL, sterile, for injection only, single-use, latex-free and non-
39 pyrogenic, commercially available in the US.
- 40 • Administer doses of HEMLIBRA greater than 1 mL and up to 2 mL with a 2 mL or 3 mL
41 syringe. A 2 mL or 3 mL syringe fulfilling the following criteria may be used: Transparent
42 polypropylene or polycarbonate syringe with Luer-Lok™ tip, graduation 0.1 mL, sterile, for
43 injection only, single-use, latex-free, and non-pyrogenic, commercially available in the US.

- 44 • A transfer needle fulfilling the following criteria may be used: Stainless steel needle with
45 Luer-Lok™ connection, sterile, 18 gauge, length 1½ inch, semi-blunted tip, single-use,
46 latex-free, and non-pyrogenic, commercially available in the US.
- 47 • An injection needle fulfilling the following criteria may be used: Stainless steel with
48 Luer-Lok™ connection, sterile, 26 gauge, maximal length ½ inch, single-use, latex-free and
49 non-pyrogenic, including needle safety feature, commercially available in the US.
- 50 • Administer each injection at a different anatomic location (upper outer arms, thighs, or any
51 quadrant of abdomen) than the previous injection. An injection should never be given into
52 moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact. Administration
53 of HEMLIBRA in the upper outer arm should only be performed by a caregiver or healthcare
54 provider.
- 55 • Discard any unused HEMLIBRA remaining in the single-dose vial.

56 **3 DOSAGE FORMS AND STRENGTHS**

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

58 Injection:

- 59 • 30 mg/mL
- 60 • 60 mg/0.4 mL
- 61 • 105 mg/0.7 mL
- 62 • 150 mg/mL

63 **4 CONTRAINDICATIONS**

64 None.

65 **5 WARNINGS AND PRECAUTIONS**

66 **5.1 Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC**

67 Cases of thrombotic microangiopathy (TMA) were reported from clinical trials when on average
68 a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate
69 (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In
70 clinical trials, thrombotic microangiopathy was reported in 1.6% of patients (3/189) and in 8.3%
71 of patients (3/36) who received at least one dose of aPCC. Patients presented with
72 thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe
73 deficiencies in ADAMTS13 activity.

74 Evidence of improvement was seen within one week following discontinuation of aPCC. One
75 patient resumed HEMLIBRA following resolution of TMA.

76 Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA
77 prophylaxis. Monitor for the development of TMA when administering aPCC. Immediately
78 discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms and/or laboratory
79 findings consistent with TMA occur, and manage as clinically indicated. Consider the benefits
80 and risks of resuming HEMLIBRA prophylaxis following complete resolution of TMA on a
81 case-by-case basis.

82 **5.2 Thromboembolism Associated with HEMLIBRA and aPCC**

83 Thrombotic events were reported from clinical trials when on average a cumulative amount of
84 >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving
85 HEMLIBRA prophylaxis. In clinical trials, thrombotic events were reported in 1.1% of patients
86 (2/189) and in 5.6% of patients (2/36) who received at least one dose of aPCC.

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

90 Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA
91 prophylaxis. Monitor for the development of thromboembolism when administering aPCC.
92 Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms,
93 imaging, or laboratory findings consistent with thromboembolism occur, and manage as
94 clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis
95 following complete resolution of thrombotic events on a case-by-case basis.

96 5.3 Laboratory Coagulation Test Interference

97 HEMLIBRA affects intrinsic pathway clotting-based laboratory tests, including activated
98 clotting time (ACT), activated partial thromboplastin time (aPTT), and all assays based on aPTT,
99 such as one-stage factor VIII (FVIII) activity (Table 1). Therefore, intrinsic pathway clotting-
100 based laboratory test results in patients treated with HEMLIBRA should not be used to monitor
101 HEMLIBRA activity, determine dosing for factor replacement or anti-coagulation, or measure
102 FVIII inhibitor titers [see *Drug Interactions (7.2)*]. Laboratory tests affected and unaffected by
103 HEMLIBRA are shown in Table 1.

104 **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)

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

106 6 ADVERSE REACTIONS

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

- 108 • Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC [see *Warnings and*
109 *Precautions (5.1)*]
- 110 • Thromboembolism Associated with HEMLIBRA and aPCC [see *Warnings and Precautions*
111 *(5.2)*]

112 6.1 Clinical Trials Experience

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

116 The following adverse reactions are based on pooled data from a randomized trial (HAVEN 1),
117 single-arm trial (HAVEN 2), and a dose-finding trial, in which a total of 189 male patients with
118 hemophilia A received at least one dose of HEMLIBRA as routine prophylaxis. Ninety-four
119 patients (50%) were adults (18 years and older), 38 (20%) were adolescents (12 years up to less
120 than 18 years), 55 (29%) were children (2 years up to less than 12 years), and two (1%) were
121 infants (1 month up to less than 2 years). Seven of the 189 patients (4%) included in the safety

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

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

126 Four patients (2.1%) in the clinical trials receiving HEMLIBRA prophylaxis withdrew from
127 treatment due to adverse reactions, which were thrombotic microangiopathy, skin necrosis and
128 superficial thrombophlebitis, and injection site reaction.

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

130 **Table 2 Adverse Reactions Reported in $\geq 5\%$ of Patients from Pooled Clinical Trials**
131 **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%)

132 * Includes injection site bruising, injection site discomfort, injection site erythema, injection site hematoma,
133 injection site induration, injection site pain, injection site pruritus, injection site rash, injection site reaction,
134 injection site swelling, injection site urticarial, and injection site warmth.

135 *Characterization of aPCC treatment in pooled clinical trials*

136 There were 125 instances of aPCC treatment in 36 patients, of which 13 instances (10.4%)
137 consisted of on average a cumulative amount of >100 U/kg/24 hours of aPCC for 24 hours or
138 more; two of the 13 were associated with thrombotic events and three of the 13 were associated
139 with TMA (Table 3). No TMA or thrombotic events were associated with the remaining
140 instances of aPCC treatment.

141 **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,b}

142 * An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there
143 was a 36-hour treatment-free break.

144 ^a Thrombotic microangiopathy

145 ^b Thrombotic event

146 *Injection Site Reactions*

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

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

151 **6.2 Immunogenicity**

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

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

164 **7 DRUG INTERACTIONS**

165 **7.1 Hypercoagulability with Concomitant Use of aPCC, rFVIIa, or FVIII**

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

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

170 **7.2 Drug-Laboratory Test Interactions**

171 HEMLIBRA restores the tenase cofactor activity of missing activated factor VIII (FVIIIa).
172 Coagulation laboratory tests based on intrinsic clotting (i.e., aPTT) measure the total clotting
173 time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic
174 pathway-based tests will yield overly shortened clotting times with HEMLIBRA, which does not
175 require activation by thrombin. The overly shortened intrinsic clotting time will then disturb all
176 single-factor assays based on aPTT, such as the one-stage FVIII activity assay; however, single-
177 factor assays utilizing chromogenic or immuno-based methods are unaffected by HEMLIBRA
178 and may be used to monitor coagulation parameters during treatment, with specific
179 considerations for FVIII chromogenic activity assays as described below.

180 Chromogenic FVIII activity tests may be manufactured with either human or bovine coagulation
181 proteins. Assays containing human coagulation factors are responsive to HEMLIBRA but may
182 overestimate the clinical hemostatic potential of HEMLIBRA. In contrast, assays containing
183 bovine coagulation factors are insensitive to HEMLIBRA (no activity measured) and can be used
184 to monitor endogenous or infused FVIII activity, or to measure anti-FVIII inhibitors.

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

189 Due to the long half-life of HEMLIBRA, effects on coagulation assays may persist for up to 6
190 months after the last dose [*see Clinical Pharmacology (12.3)*].

191 **8 USE IN SPECIFIC POPULATIONS**

192 **8.1 Pregnancy**

193 Risk Summary

194 There are no available data on HEMLIBRA use in pregnant women to inform a drug-associated
195 risk of major birth defects and miscarriage. Animal reproduction studies have not been
196 conducted with emicizumab-kxwh. It is not known whether HEMLIBRA can cause fetal harm
197 when administered to a pregnant woman or can affect reproduction capacity. HEMLIBRA
198 should be used during pregnancy only if the potential benefit for the mother outweighs the risk to
199 the fetus.

200 All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The
201 estimated background risk of major birth defects and miscarriage for the indicated populations is
202 unknown. In the U.S. general population, the estimated background risk of major birth defect and
203 miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

204 **8.2 Lactation**

205 Risk Summary

206 There is no information regarding the presence of emicizumab-kxwh in human milk, the effects
207 on the breastfed child, or the effects on milk production. Human IgG is known to be present in
208 human milk. The developmental and health benefits of breastfeeding should be considered along
209 with the mother’s clinical need for HEMLIBRA and any potential adverse effects on the
210 breastfed child from HEMLIBRA or from the underlying maternal condition.

211 **8.3 Females and Males of Reproductive Potential**

212 Contraception

213 Women of childbearing potential should use contraception while receiving HEMLIBRA.

214 **8.4 Pediatric Use**

215 The safety and efficacy of HEMLIBRA have been established in pediatric patients. Use of
216 HEMLIBRA in pediatric patients with hemophilia A with FVIII inhibitors is supported by a
217 randomized trial (HAVEN 1) and a single-arm trial (HAVEN 2). HAVEN 1 included pediatric
218 patients in the following age group: 38 adolescents (12 years to less than 18 years). HAVEN 2
219 included pediatric patients in the following age groups: 55 children (2 years up to less than 12
220 years) and two infants (1 month up to less than 2 years). No differences in efficacy were
221 observed between the different age groups [*see Clinical Studies (14)*].

222 In general, the adverse reactions in HEMLIBRA-treated pediatric patients were similar in type to
223 those seen in adult patients with hemophilia A with FVIII inhibitors [*see Adverse Reactions*
224 (6.1)].

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

227 **8.5 Geriatric Use**

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

230 **11 DESCRIPTION**

231 Emicizumab-kxwh is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody
232 with a bispecific antibody structure binding factor IXa and factor X. Emicizumab-kxwh has an
233 approximate molecular weight of 145.6 kDa and is produced in genetically engineered
234 mammalian (Chinese hamster ovary) cells. Emicizumab-kxwh has no structural relationship or

235 sequence homology to FVIII and, as such, does not induce or enhance the development of direct
236 inhibitors to FVIII.

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

240 Each single-dose 30 mg vial contains a 1 mL solution of emicizumab-kxwh (30 mg), L-arginine
241 (26.1 mg), L-histidine (3.1 mg), and poloxamer 188 (0.5 mg), adjusted to pH 6.0 with L-aspartic
242 acid.

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

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

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

252 **12 CLINICAL PHARMACOLOGY**

253 **12.1 Mechanism of Action**

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

256 **12.3 Pharmacokinetics**

257 Emicizumab-kxwh exhibited dose-proportional pharmacokinetics over a dose range of 0.3 mg/kg
258 (0.1 times approved recommended starting dosage) to 3 mg/kg once weekly following
259 subcutaneous administration. Following multiple subcutaneous administrations of 3 mg/kg once
260 weekly for the first 4 weeks in hemophilia A patients, mean (\pm SD) trough plasma concentrations
261 of emicizumab-kxwh increased to achieve 54.6 ± 14.3 μ g/mL at Week 5. Trough plasma
262 concentrations above 50 μ g/mL were sustained thereafter with the recommended weekly dosage
263 of 1.5 mg/kg; the mean (\pm SD) trough plasma concentrations of emicizumab-kxwh at steady-
264 state was 52.8 ± 13.5 μ g/mL.

265 Absorption

266 Following subcutaneous administration, the mean (\pm SD) absorption half-life was 1.7 ± 1 day.

267 The absolute bioavailability following subcutaneous administration of 1 mg/kg was between
268 80.4% and 93.1%. Similar pharmacokinetic profiles were observed following subcutaneous
269 administration in the abdomen, upper arm, and thigh [*see Dosage and Administration (2.2)*].

270 Distribution

271 The mean apparent volume of distribution was 11.4 L (95% confidence interval (CI) [10.6,
272 12.1]).

273 Elimination

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

276 Specific Populations

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

279 hepatic impairment (defined as total bilirubin 1x to $\leq 1.5x$ the upper limit of normal (ULN) and
280 any aspartate transaminase (AST) level) and moderate hepatic impairment (defined as total
281 bilirubin 1.5x to $\leq 3x$ the ULN and any AST level).

282 *Body weight:* The apparent clearance and volume of distribution of emicizumab-kxwh increased
283 with increasing body weight (14.2 kg to 131 kg). Dosing in mg/kg provides similar emicizumab-
284 kxwh exposure across body weight range.

285 Drug Interaction Studies

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

287 **13 NONCLINICAL TOXICOLOGY**

288 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

291 Animal fertility studies have not been conducted; however, emicizumab-kxwh did not cause any
292 toxicological changes in the reproductive organs of male or female cynomolgus monkeys at
293 doses of up to 30 mg/kg/week in subcutaneous general toxicity studies of up to 26-week duration
294 and at doses of up to 100 mg/kg/week in a 4-week intravenous general toxicity study.

295 **14 CLINICAL STUDIES**

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

299 HAVEN 1

300 The HAVEN 1 study (NCT02622321) was a randomized, multicenter, open-label, clinical trial in
301 109 adult and adolescent males (aged 12 to 75 years and > 40 kg) with hemophilia A with FVIII
302 inhibitors who previously received either episodic (on-demand) or prophylactic treatment with
303 bypassing agents. Patients received weekly HEMLIBRA prophylaxis (Arms A, C, and D),
304 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter, or no
305 prophylaxis (Arm B). Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on
306 HEMLIBRA prophylaxis in case of suboptimal efficacy (i.e., ≥ 2 spontaneous and clinically
307 significant bleeds). During the study, two patients underwent up-titration of their maintenance
308 dose to 3 mg/kg once weekly.

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

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

319 Efficacy was evaluated based on the annualized bleeding rate (ABR) requiring treatment with
320 coagulation factors (minimum of 24 weeks or date of discontinuation) among patients previously
321 treated with episodic bypassing agents who were randomized to HEMLIBRA prophylaxis (Arm
322 A) compared with those receiving no prophylaxis (Arm B). The trial also evaluated the
323 randomized comparison of Arms A and B for the efficacy of weekly HEMLIBRA prophylaxis in

324 reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds, as
325 well as patient-reported symptoms and physical functioning.

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

331 The efficacy results of HEMLIBRA prophylaxis compared with no prophylaxis in bleed rate for
332 treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint
333 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)

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

338 ^a Based on negative binomial regression.

339 In the intra-patient analysis, HEMLIBRA prophylaxis resulted in a statistically significant
340 (p=0.0003) reduction (79%) in bleed rate for treated bleeds compared with previous bypassing
341 agent prophylaxis collected in the NIS prior to enrollment (Table 5).

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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)

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

^a Based on negative binomial regression.

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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.

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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	

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^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.

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HAVEN 2

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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.

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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).

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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.

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

375 **Table 7 Annualized Bleed Rate with HEMLIBRA Prophylaxis in Pediatric**
 376 **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)

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

379 * No treated target joint bleeds reported

380 ^a Based on negative binomial regression

381 In the intra-patient analysis, 13 pediatric patients who had participated in the NIS had an ABR of
 382 17.2 (95% CI [12.4, 23.8]) on previous bypassing agent treatment (prophylactic treatment in 12
 383 patients and on-demand treatment for one patient). Weekly HEMLIBRA prophylaxis resulted in
 384 an ABR for treated bleeds of 0.2 (95% CI [0.1, 0.8]) based on negative binomial regression,
 385 corresponding to a 99% reduction in bleed rate. On HEMLIBRA prophylaxis, 11 patients
 386 (84.6%) had zero treated bleeds.

387 **16 HOW SUPPLIED/STORAGE AND HANDLING**

388 How Supplied

389 HEMLIBRA (emicizumab-kxwh) injection is available as a sterile, preservative-free, colorless to
 390 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

391 Storage and Handling

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

400 **17 PATIENT COUNSELING INFORMATION**

401 Advise the patient to read the FDA-approved patient labeling (Patient Information and
402 Instructions for Use).

403 Use of Bypassing Agents

404 Inform the patient and/or caregiver that HEMLIBRA increases coagulation potential. Advise the
405 patient and/or caregiver to discontinue prophylactic use of bypassing agents the day before
406 starting HEMLIBRA prophylaxis. Discuss the use of bypassing agents with the patient and/or
407 caregiver prior to starting HEMLIBRA prophylaxis [*see Adverse Reactions (6.1)*].

408 Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

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

414 Thromboembolism Associated with HEMLIBRA and aPCC

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

420 Laboratory Coagulation Test Interference

421 Inform the patient and/or caregiver that HEMLIBRA interferes with some laboratory tests that
422 measure blood clotting and may cause a false reading. Advise the patient and/or caregiver that
423 they should notify any healthcare provider about this possibility prior to any blood tests or
424 medical procedures [*see Warnings and Precautions (5.3)*].

425 Instruction on Injection Technique

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

430 Advise the patient to follow the recommendations in the FDA-approved patient labeling
431 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

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Chugai Pharmaceutical Co., Ltd., Tokyo, Japan
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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. 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

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

Instructions for Use
HEMLIBRA® (hem-lee-bruh)
(emicizumab-kxwh)
injection, for subcutaneous use

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

Important Information:

- **Do not** inject yourself or someone else unless you have been shown how to by your healthcare provider.
- Make sure the name HEMLIBRA appears on the box and vial label.
- Before opening the vial, read the vial label to make sure you have the medicine strength(s) needed to give the dose prescribed by your healthcare provider.
- HEMLIBRA comes in four strengths. Depending on your dose, you may need to use more than one vial to give your total prescribed dose. Your healthcare provider will determine your dose in milliliters (mL) that you will need to give based on your body weight. **Do not use different HEMLIBRA vials of different concentrations** when combining vials to achieve the prescribed dose.
- Check the expiration date on the box and vial label. **Do not** use if the expiration date has passed.
- **Only use the vial one time.** After you inject your dose, dispose of (throw away) any unused HEMLIBRA left in the vial. Do not save unused HEMLIBRA in the vial for later use.
- **Only use the syringes, transfer needles, and injection needles that your healthcare provider prescribes.**
- **Only use the syringes, transfer needles and injection needles one time. Dispose of (throw away) any used syringes and needles.**
- If your prescribed dose is more than 2 mL, you will need to give more than one injection of HEMLIBRA.

Storing 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.
- Take the vial out of the refrigerator 15 minutes before use and allow it to reach room temperature before preparing an injection.
- Before giving the injection, unopened vials of HEMLIBRA may 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 **or**
 - at a temperature greater than 86°F (30°C)

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

Inspecting the HEMLIBRA vial and your supplies:

- Collect all supplies listed below to prepare and give your injection.
- **Check** the expiration date on the box, on the vial label, and on the supplies listed below. **Do not use** if the expiration date has passed.
- Inspect the supplies for damage. **Do not use** if they appear damaged or if they have been dropped.
- Place the supplies on a clean, well-lit flat work surface.

HEMLIBRA is colorless to slightly yellow in color. Do not use the vial if:

- the medicine is cloudy, hazy, or colored.
- the medicine contains particles.
- the cap covering the stopper is missing.

Included in the box:

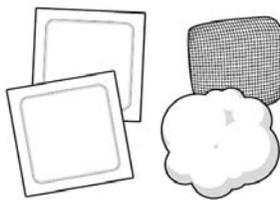


- **Vial containing HEMLIBRA**

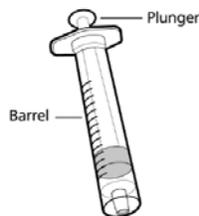


- **HEMLIBRA Instructions for Use**

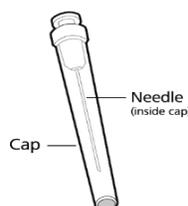
Not included in the box:



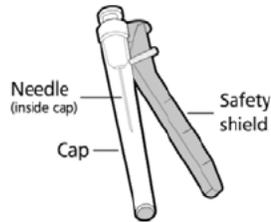
- **Alcohol wipes**
Note: If you need to use more than one vial to inject your prescribed dose, you must use a new alcohol wipe for each vial.
- **Gauze**
- **Cotton Ball**



- **Syringe**
Note: For injection amount up to 1 mL, use a **1 mL syringe**. For injection amount between 1 mL and 2 mL, use a **2 mL or 3 mL syringe**.



- **18G Transfer Needle**
Note: If you need to use more than one vial to inject your prescribed dose, you must use a new transfer needle for each vial. **Do not** use the transfer needle to inject HEMLIBRA.



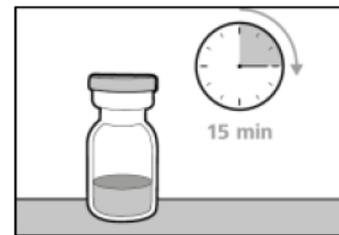
- **26G Injection Needle with safety shield**
Do not use the injection needle to withdraw HEMLIBRA from vial.



- **Sharps disposal container**

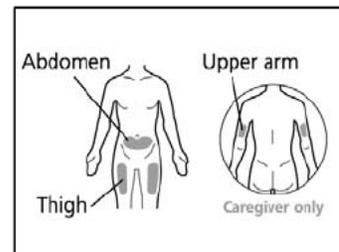
Get ready:

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



Selecting and preparing an injection site:

- Clean the chosen injection site area using an alcohol wipe.
- Let the skin dry for about 10 seconds. Do not touch, fan, or blow on the cleaned area before your injection.
- **You can use your:**
 - Thigh (front and middle).
 - Stomach area (abdomen), except for 2 inches around the navel (belly button).
 - Outer area of the upper arm (only if a caregiver is giving the injection).
- You should use a different injection site each time you give an injection, at least 1 inch away from the area you used for your previous injection.
- Do not inject into areas that could be irritated by a belt or waistband. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or the skin is broken.



Preparing the syringe for injection:

- HEMLIBRA must not be stored **in the syringe**.
- HEMLIBRA in the syringe must be injected under the skin (subcutaneous injection) immediately.
- **Dispose of (throw away) any used vial(s), needles, vial and injection needle caps, and used syringes in a sharps or puncture-proof container.**

Important information after the injection:

- Do not rub the injection site after an injection.
- If you see drops of blood at the injection site, you can press a sterile cotton ball or gauze over the injection site for at least 10 seconds, until bleeding has stopped.
- If you have bruising (small area of bleeding under the skin), an ice pack can also be applied with gentle pressure to the site. If bleeding does not stop, please contact your healthcare provider.

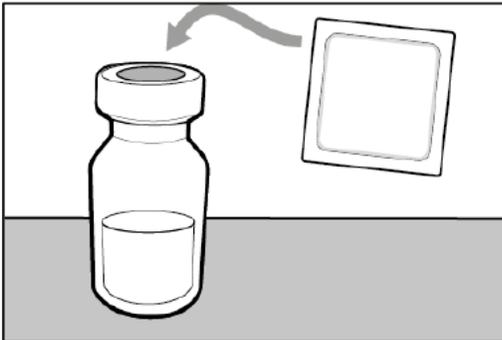
Disposing of used HEMLIBRA vial(s), needles, and syringes:

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not dispose of (throw away) any loose needles and syringes in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of heavy-duty plastic.
 - can be closed with a tight-fitting, puncture resistant lid, without sharps being able to come out.
 - upright and stable during use.
 - leak-resistant.
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of (throw away) any used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

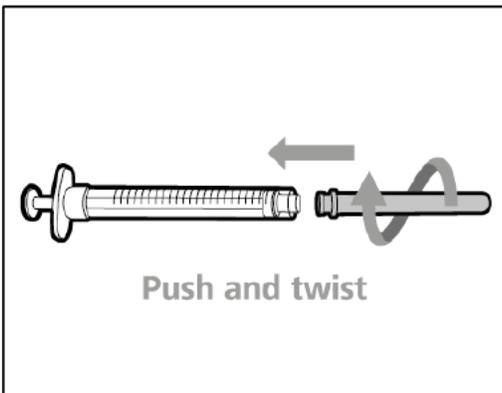
Important: Always keep the sharps disposal container out of reach of children.

Step 1. Remove vial cap and clean top

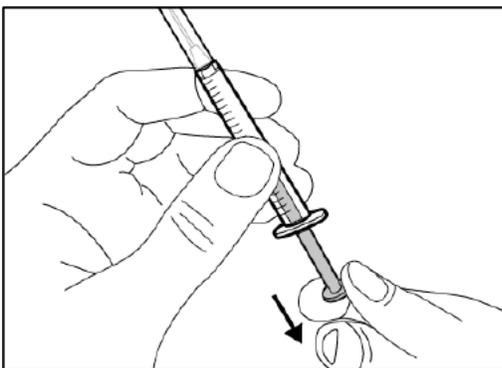
- Take the cap off the vial(s).



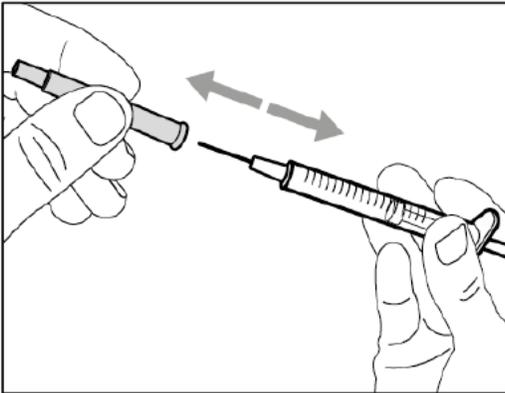
- Clean the top of the vial(s) stopper with an alcohol wipe.
- Dispose of (throw away) the vial cap(s) into the sharps disposal container.

Step 2. Attach transfer needle to syringe

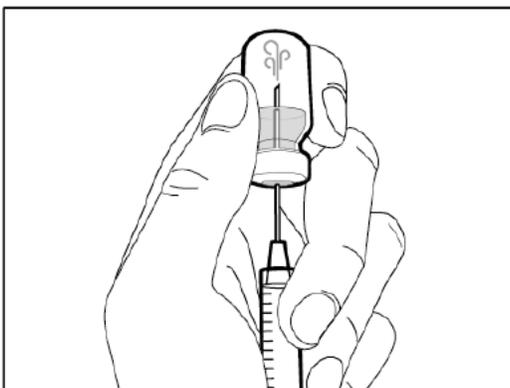
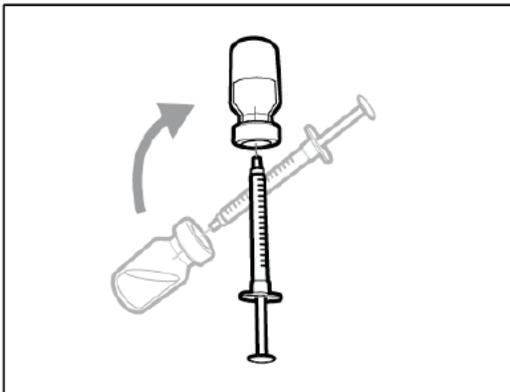
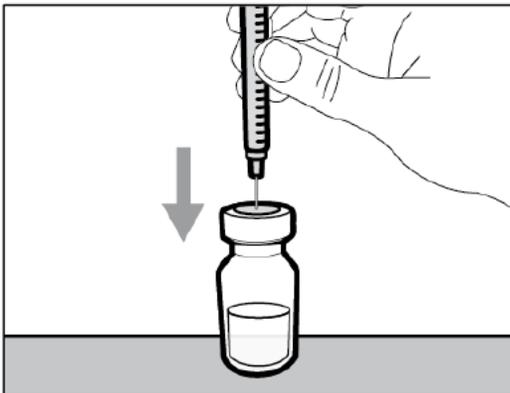
- **Push and twist the transfer needle clockwise** on to the syringe until it is fully attached.



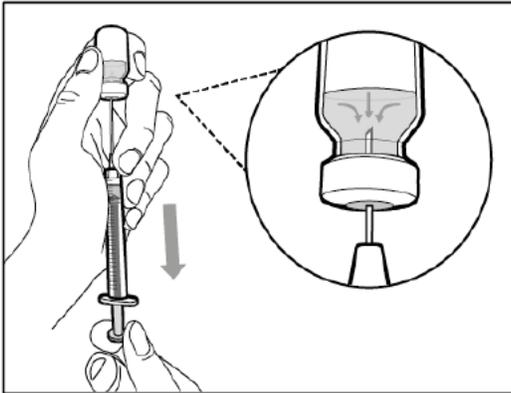
- Slowly pull back on the plunger and draw air into the syringe that is the same amount for your prescribed dose.

Step 3. Uncap transfer needle

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

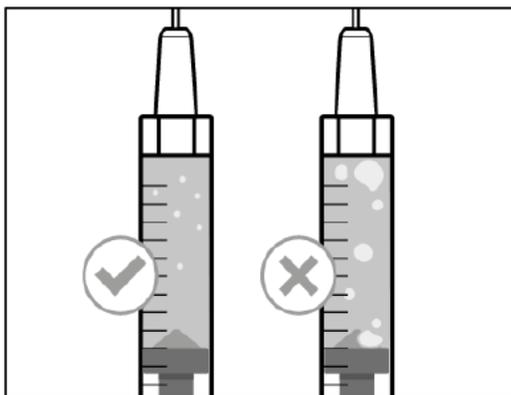
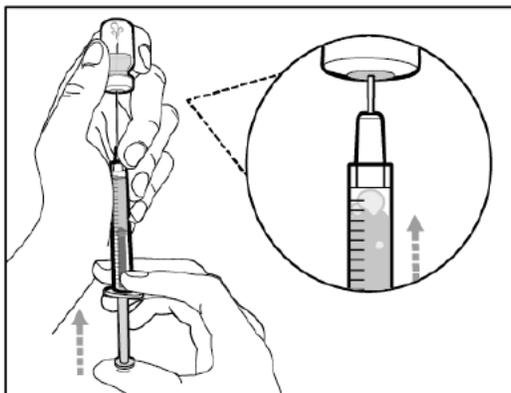
Step 4. Inject air into vial

- Keep the vial on the flat working surface and insert the transfer needle and syringe straight down into the **center** of the vial stopper.
- Keep the needle in the vial and turn the vial upside down.
- With the needle pointing upwards, push on the plunger to inject the air from the syringe **above the medicine**.
- Keep your finger pressed down on the syringe plunger.
- **Do not** inject air into the medicine.

Step 5. Transfer HEMLIBRA to syringe

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

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

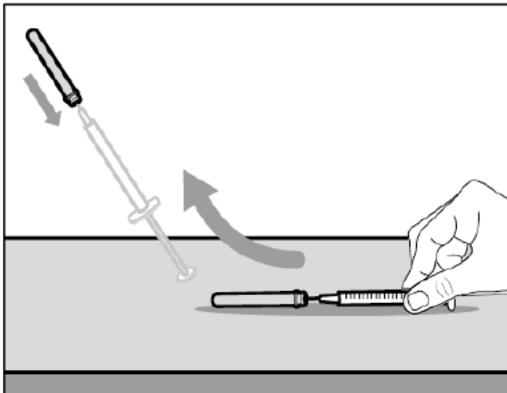
Step 6. Remove air bubbles

- Keep the needle in the vial and check the syringe for larger air bubbles. Too large an air bubble can reduce the dose you receive.
- **Remove the larger air bubbles** by gently tapping the syringe barrel with your fingers until the air bubbles rise to the top of the syringe. Move the tip of the needle **above the medicine** and slowly push the plunger up to push the air bubbles out of the syringe.
- If the amount of HEMLIBRA in the syringe is now at or below your prescribed dose, move the tip of the needle to **within the medicine** and slowly **pull back** the plunger until you have **more** than the amount of HEMLIBRA needed for your **prescribed dose**.
- Be careful not to pull the plunger out of the syringe.
- Repeat the steps above until you have removed the larger air bubbles.

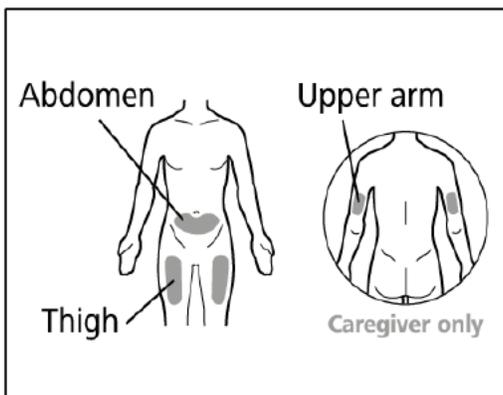
Note: Ensure you have enough HEMLIBRA in the syringe to complete your dose before moving on to the next step. If you cannot remove all of HEMLIBRA, turn the vial upright to reach the remaining amount.



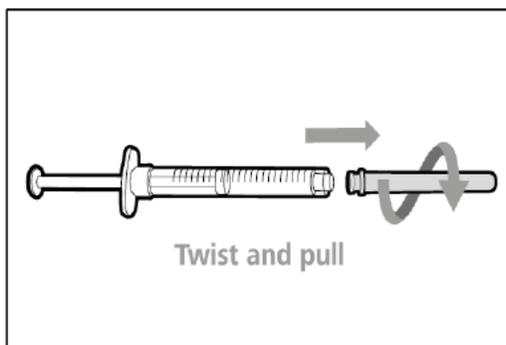
Do not use the transfer needle to inject HEMLIBRA as this may cause harm such as pain and bleeding.

Step 7. Recap transfer needle

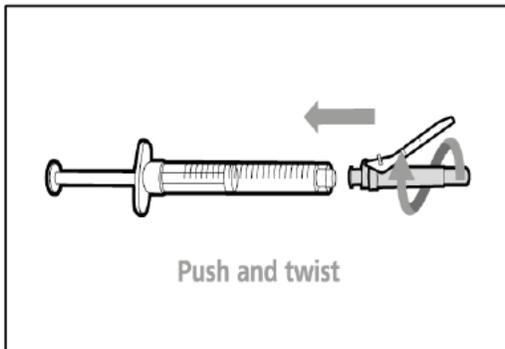
- Remove the syringe and transfer needle from the vial.
- **Using one hand, slide** the transfer needle into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle cap towards the syringe to fully attach it with **one hand** to prevent accidentally sticking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

Step 8. Clean injection site

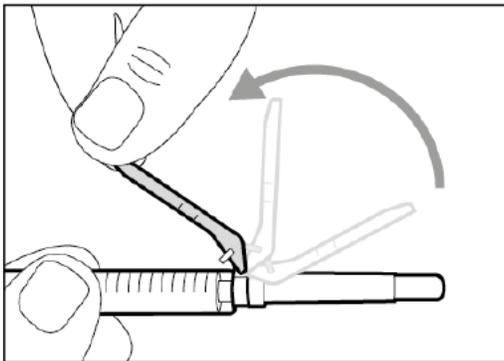
- Select and **clean** your injection site with an alcohol wipe.
- Let the skin dry for about 10 seconds. Do not touch, fan, or blow on the cleaned area before your injection.

Step 9. Remove transfer needle

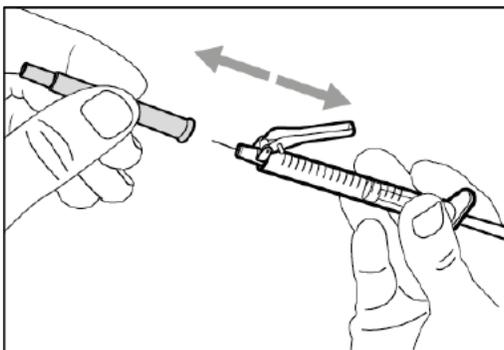
- Remove the transfer needle from the syringe by twisting counter-clockwise and gently pulling.
- Dispose of (throw away) the used transfer needle into a sharps disposal container.

Step 10. Attach injection needle to syringe

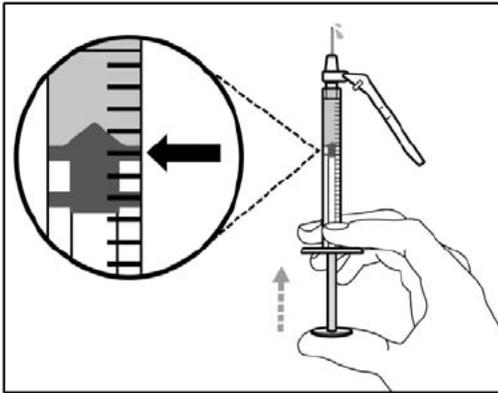
- Push and twist the injection needle clockwise on to the syringe until it is fully attached.

Step 11. Move safety shield

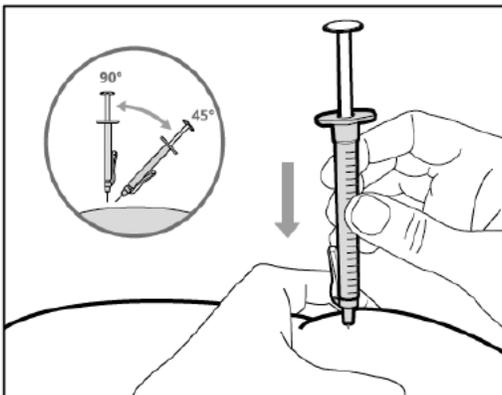
- Move the safety shield away from the needle and **towards** the syringe barrel.

Step 12. Uncap injection needle

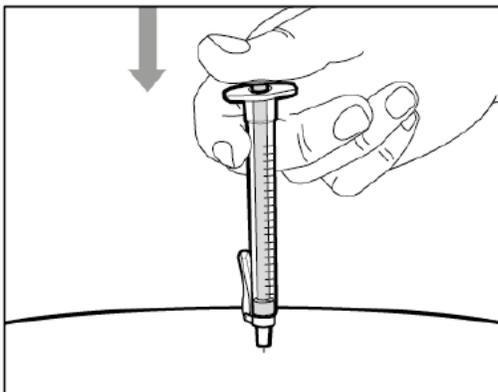
- Carefully pull the injection needle cap away from the syringe.
- Dispose of (throw away) the cap into a sharps disposal container.
- **Do not touch** the needle tip or allow it to touch any surface.
- After the injection needle cap has been removed, HEMLIBRA in the syringe must be injected immediately.

Step 13. Adjust plunger to prescribed dose

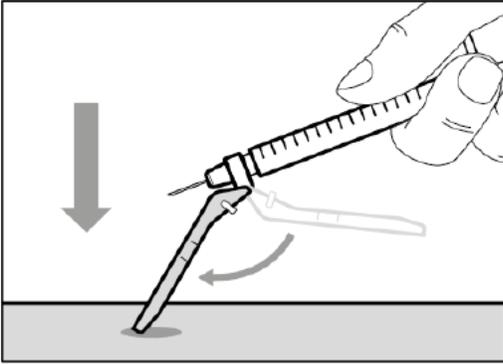
- Slowly push the plunger to your prescribed dose.
- Ensure the top rim of the plunger is in line with the mark on the syringe for your prescribed dose.

Step 14. Subcutaneous (under the skin) injection

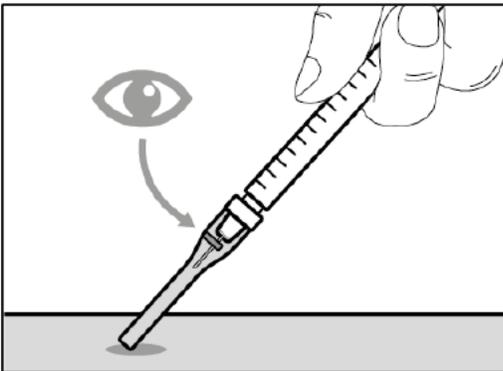
- Pinch the selected injection site and fully insert the needle at a **45° to 90° angle** with a quick, firm action. **Do not** hold or push on the plunger while inserting the needle.
- Hold the position of the syringe and let go of the pinched injection site.

Step 15. Inject HEMLIBRA

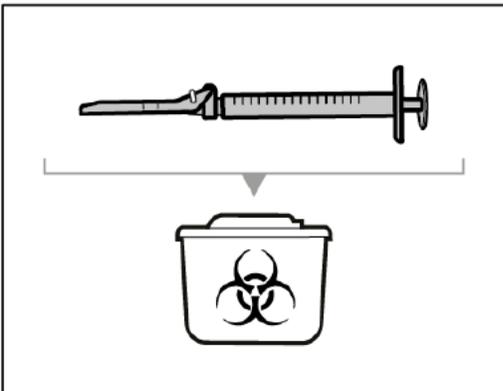
- Slowly inject all of HEMLIBRA by gently pushing the plunger all the way down.
- Remove the needle and syringe from the injection site at the same angle as inserted.

Step 16. Cover needle with safety shield

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



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

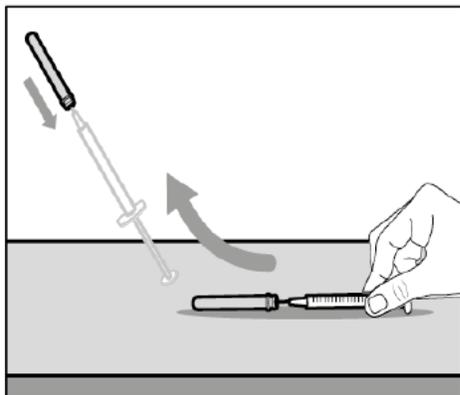
Step 17. Dispose of (throw away) the used HEMLIBRA vial(s), needle, and syringe

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. For further information, refer to the section “Disposing of used HEMLIBRA vial(s), needles, and syringes”.
- **Do not** try to remove the used injection needle from the used syringe.
- **Do not recap** the injection needle with the cap.
- **Important:** Always keep the sharps disposal container out of reach of children.
- Dispose of (throw away) any used vial(s), needles, vial and injection needle caps, and used syringes in a sharps or puncture-proof container.

Combining Vials

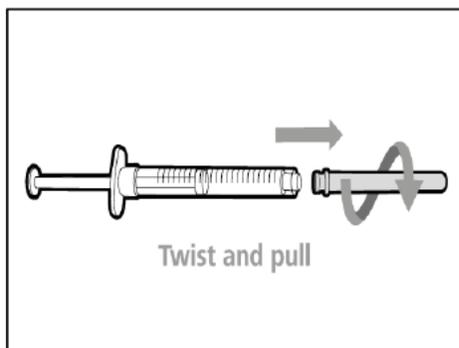
If you need to use more than one vial to get to your total prescribed dose, follow these steps after you have drawn up HEMLIBRA from the first vial:

Step A. Recap transfer needle



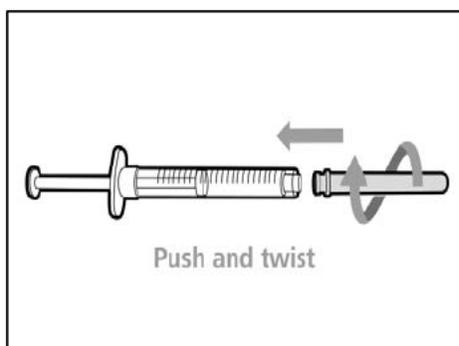
- Remove the syringe and transfer needle from the first vial.
- **Using one hand**, slide the transfer needle into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle cap toward the syringe to fully attach it with **one hand** to prevent accidentally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

Step B. Remove transfer needle



- Remove the transfer needle from the syringe by twisting counter-clockwise and gently pulling.
- Dispose of (throw away) the used transfer needle into a sharps disposal container.

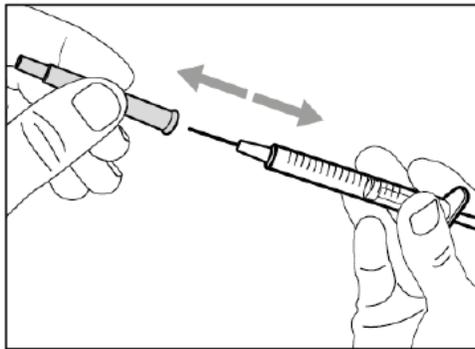
Step C. Attach a new transfer needle to syringe



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

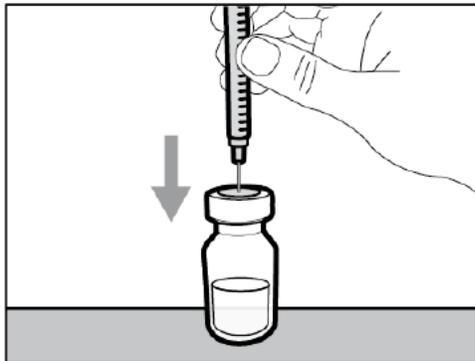
- Push and twist a **new** transfer needle clockwise on to the syringe until it is fully attached.
- Slowly pull back the plunger and draw some air into the syringe.

Step D. Uncap transfer needle

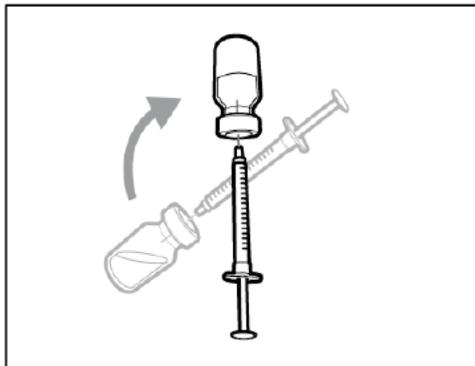


- Hold the syringe by the barrel with the transfer needle cap pointing up.
- Carefully pull the transfer needle cap straight off and away from your body. **Do not throw the cap away.** You will need to recap the transfer needle after drawing up the medicine.
- **Do not touch** the needle tip.

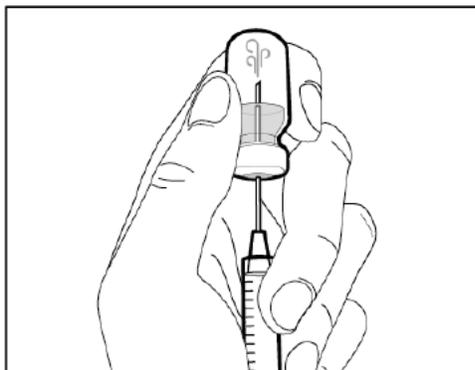
Step E. Inject air into vial



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

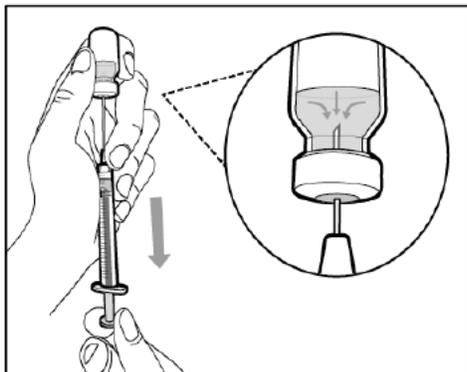


- Keep the transfer needle in the vial and turn the vial upside down.



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

Step F. Transfer HEMLIBRA to syringe



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

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

! Do not use the transfer needle to inject HEMLIBRA as this may cause harm such as pain and bleeding.

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

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

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/s/

RICHARD PAZDUR
11/16/2017