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Supplemental information

Advances in biopharmaceutical products for hemophilia

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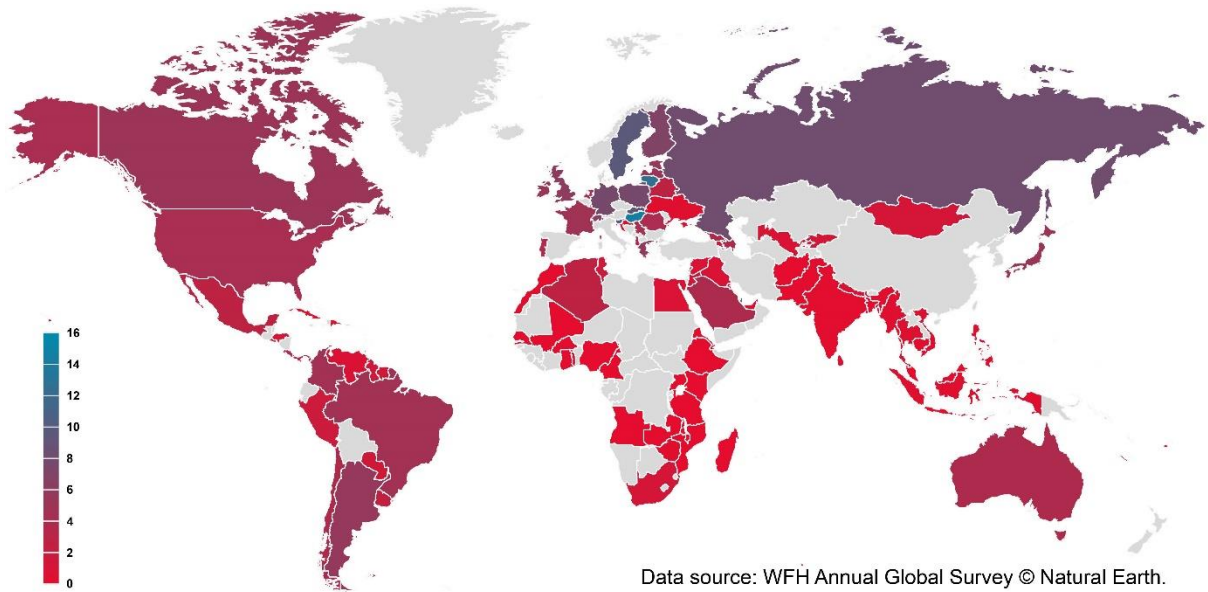
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17 **Figure S1. World map of coagulation factor VIII (FVIII) use per capita in 2022.** FVIII per
18 capita serves as a general indicator of treatment levels owing to being the largest expenditure
19 in all care systems. Gray indicates no data reported for 2022. Data source: WFH Annual Global
20 Survey © Natural Earth.

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22 **Table S1. Clinical application characteristics of licensed biopharmaceuticals for hemophilia**

Category/product Approval information	Patient population	Age group	Half-life	Administration frequency and dosage		
				Prophylaxis	Episodic treatment	Perioperative management
Plasma-derived FVIII						
Alphanate 1978 USA	PwHA without inhibitors	Adults	17.9 h.	Not indicated	Minor, moderate, and major BE: twice daily, 15, 25, and 40–50 IU/kg (30, 50, and 80–100 IU/dL), respectively. ^a	Minor and major surgeries: twice daily. Initially, 40–50 IU/kg (80–100 IU/dL); the next 7–10 days, 30–50 IU/kg (60–100 IU/dL). ^a
Hemofil M 2001 USA	PwHA without inhibitors; PTPs and PUPs	Adults and children	14.8 h	Not indicated	Early, and more extensive BE: every 12–24 h, 20–40, and 30–60 IU/dL, respectively. Life-threatening BE: every 8–24 h, 60–100 IU/dL.	Minor surgery: one single infusion, 60–80 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Humate-p 1981 Germany	PwHA without inhibitors	Adults	12.2 h.	Not indicated	Minor BE: once or twice daily, 15 IU/kg (30 IU/dL). ^a	Minor surgery: loading dose 25 IU/kg (50 IU/dL); followed by 15 IU/kg (30

Wilate 2009 USA	PwHA without inhibitors	Adults and adolescents	Adults: OSA, 10.6 h. Adolescent (12–15 y): OSA, 11.4 h.	Every 2–3 days, 20–40 IU/kg.	Moderate BE: loading dose, 25 IU/kg (50 IU/dL); followed by 15 IU/kg (30 IU/dL) every 8–12 h for 1–2 days. Then once or twice daily for up to 7 days, 15 IU/kg (30 IU/dL). ^a Major surgery: initially 40– 50 IU/kg (80–100 IU/dL), followed by 20–25 IU/kg (40–50 IU/dL) every 8 h for 7 days; then, once or twice daily for 7 days, 20–25 IU/kg (40–50 IU/dL). ^a Life-threatening BE: initially 40–50 IU/kg (80–100 IU/dL), followed by 20–25 IU/kg (40–50 IU/dL) every 8 h for 7 days. Then, once or twice daily for 7 days, 20–25 IU/kg (40–50 IU/dL). ^a Minor and moderate BE: every 12–24 h, 30–40 IU/kg (60–80 IU/dL). ^a Major BE: every 12–24 h, 35–50 IU/kg (70–100 IU/dL). ^a	Not indicated
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Plasma-derived FIX

					Life-threatening BE: every 8–24 h, 35–50 IU/kg (70–100 IU/dL). ^a	
AlphaNine SD 1990 USA	PwHB without inhibitors; PTPs and PUPs.	Adults	21 h	Not indicated	Minor and moderate BE: twice daily, 20–30 and 25–50 IU/kg (20–30 and 25–50 IU/dL), respectively. ^b Major BE: twice daily, 30–50 IU/kg (30–50 IU/dL) at least 3–5 days; then, 20 IU/kg (20 IU/dL). ^b	Minor and major surgeries: twice daily, 50–100 IU/kg (50–100 IU/dL). ^b
Haemonine 2008 Germany	PwHB without inhibitors	Adults, adolescents, and children (≥ 6 y)	Adults: OSA, 27.6 h	Interval of every 3–4 days, 20–40 IU/kg.	Early and more extensive BE: every 24 h, 20–40 and 30–60 IU/dL, respectively. Life-threatening BE: every 8–24 h, 60–100 IU/dL.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Nonafact 2001 EU	PwHB without inhibitors; PTPs	Adults, adolescents, and children (≥ 6 y)	19 h	Interval of every 3–4 days, 20–40 IU/kg.	Early and more extensive BE: every 24 h, 20–40 and 30–60 IU/dL, respectively.	Minor surgery: every 24 h, 30–60 IU/dL.

					Life threatening: every 8–24 h, 60–100 IU/dL.	Major surgery: every 8–24 h, 80–100 IU/dL.
Octanine F 2002 EU	PwHB without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults, adolescents: 29.1 h	Interval of every 3–4 days, 20–40 IU/kg	Early and more extensive BE: every 24 h, 20–40 and 30–60 IU/dL, respectively. Life threatening: every 8–24 h, 60–100 IU/dL.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Recombinant FVIII (SHL)						
Kogenate FS (FL) 1993 USA	PwHA without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults and adolescents (12–33 y): OSA, 13.7–14.6 h. Children (4.4–18.1 y): OSA, 10.7 h.	Adults and adolescents: 3 times weekly, 25 IU/kg. Children: every other day, 25 IU/kg.	Minor BE: repeat dose if there is evidence of further bleeding, 20–40 IU/dL. Moderate BE: every 12–24 h, 30–60 IU/dL. Major BE: every 8–12 h. Initial: 80–100 IU/dL; repeat: 40–50 IU/dL.	Minor surgery: every 12–24 h, 30–60 IU/dL. Major surgery: every 6–12 h, 100 IU/dL.
Octocog alfa (FL) 2003 USA	PwHA without inhibitors; PTPs and PUPs	All age groups	Adults: OSA, 12.9 h. Adolescents: OSA, 12.1 h.	Adults, adolescents, and OC: interval of every 2–3 days, 20–40 IU/kg	Minor and moderate BE: every 12–24 h (adults, adolescents, and OC), 8–12 h	Minor surgery: every 24 h (adults, adolescents, and OC), or every 12–24 h (SC); 30–60 IU/dL.

			Children (2–12 y): OSA, 9.6–11.8 h. Infants (1 month to < 2 y): OSA, 9.0 h.	SC: 3–4 times weekly, 20–50 IU/kg.	(SC); 20–40, and 30–60 IU/dL, respectively. Major BE: every 8–24 h (adults, adolescents, and OC), 6–12 h (SC), 60–100 IU/dL.	Major surgery: every 8–24 h (adults, adolescents, and OC), every 6–24 h (SC); 80– 100 IU/dL.
Recombinate (FL) 1992 USA	PwHA without inhibitors; PTPs and PUPs	Adults, adolescents, and children	14.6 h	Not indicated	Early and more extensive BE: every 12–24 h, 20–40 and 30–60 IU/dL, respectively. Life threatening: every 8–24 h, 60–100 IU/dL.	Minor surgery: a single infusion, 60–80 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Simoctocog alfa (BDD) 2015 USA	PwHA without inhibitors; PTPs	Adults, adolescents, and children (≥ 2 y)	Adults and adolescents: OSA, 17.1 h. Children: OSA, 11.9–13.1 h.	Adults and adolescents: every other day, 30–40 IU/kg. Children: 3 times weekly or every other day, 30–50 IU/kg.	Minor and moderate to major BE: every 12–24 h, 20–40 and 30–60 IU/dL, respectively. Life-threatening BE: every 8–24 h, 60–100 IU/dL.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.

Turoctocog alfa (BDT) 2013 USA	PwHA without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults and adolescents: OSA, 10.8–12.8 h; TSA, 12.0–12.4 h. Children: OSA, 7.7– 8.0 h; TSA, 9.4–10.0 h.	Adults and adolescents: 3 times weekly, 20–50 IU/kg; or every other day, 20–40 IU/kg. Children: 3 times weekly, 25–60 IU/kg; or every other day, 25–50 IU/kg.	Minor, and moderate BE: every 12–24 h, 20–40 and 30–60 IU/dL, respectively. Major BE: every 8–24 h, 60– 100 IU/dL.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Recombinant FVIII (EHL, including efanesoctocog alfa)						
Damoctocog alfa pegol (BDD, PEGylated) 2018 USA	PwHA without inhibitors; PTPs	Adults and adolescents	OSA, 17.4–21.4 h. TSA, 17.9–18.6 h.	Every 5 days, 45–60 IU/kg; every 7 days, 60 IU/kg; or twice weekly, 30–40 IU/kg	Minor and moderate BE: every 24–48 h, 20–40, and 30–60 IU/dL, respectively. Major BE: every 8–24 h, 60– 100 IU/dL.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 12–24 h, 80–100 IU/dL.
Efanesoctocog alfa (BDD, Fc-vWF-XTEN fusion protein) 2023 USA	PwHA without inhibitors; PTPs	Adults, adolescents, and children ^c	Adults: OSA, 48.2 h. Adolescents: OSA, 44.6 h. Children (1–12 y): OSA, 33.9–42.4 h.	Once weekly, 50 IU/kg	Minor, moderate, and major BE: every 2–3 days, 30–50 IU/kg (60–100 IU/dL). ^a	Minor and major surgeries: every 2–3 days, 30–50 IU/kg (60–100 IU/dL). ^a

Efmoroctocog alfa (BDD, Fc fusion protein) 2014 USA	PwHA without inhibitors; PTPs	Adults, adolescents, and children (≥ 1 y)	Adults: 19.7 h. Adolescents: 16.4 h. Children: 12.7–14.9 h.	Adults, adolescents and OC: 3–5 day intervals, 25–65 IU/kg. SC: twice weekly, then 3–5 day intervals; 25–65 IU/kg.	Minor and moderate BE: every 24–48 h (adults, adolescents, and OC) or every 12–24 h (SC); 40–60 IU/dL. Major BE: every 12–24 h (adults, adolescents, and OC), or every 8–24 h (SC); 80–100 IU/dL.	Minor surgery: every 24 h (adults, adolescents, and OC), or every 12–24 h (SC); 50–80 IU/dL. Major surgery: every 8–24 h (adults, adolescents, and OC) or every 6–24 h (SC); 80– 120 IU/dL.
Lonoctocog alfa (BDT, Single-chain) 2016 USA	PwHA without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults: TSA, 14.2 h. Adolescents: TSA, 14.3 h. Children: TSA, 10.2–10.4 h.	2–3 times weekly. Adults and adolescents: 20–50 IU/kg; children: 30–50 IU/kg.	Minor and moderate BE: every 12–24 h; 20–40 and 30–60 IU/dL, respectively. Major/life-threatening BE: every 8–24 h, 60–100 IU/dL.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Rurioctocog alfa pegol (FL, PEGylated) 2015 USA	PwHA without inhibitors; PTPs and PUPs	Adults, adolescents, and children (≥ 1 y)	Adults: OSA, 14.7 h. Adolescents: OSA, 13.4 h. Children (2–12 y): OSA, 11.8–12.4 h.	Twice weekly. Adults and adolescents: 40–50 IU/kg; children: 55 IU/kg.	Minor and moderate BE: every 12–24 h, 20–40 and 30–60 IU/dL, respectively. Major BE: every 8–24 h, 60– 100 IU/dL.	Minor surgery: every 24 h, 60–100 IU/dL. Major surgery: every 8–24 h (adults and adolescents) or every 6–24 h (children); 80– 120 IU/dL.

					Minor BE: one dose, 40 IU/kg (80 IU/dL) for adults and adolescents) or 65 IU/kg (130 IU/dL) for children. ^a	Minor surgery: additional dose(s) after 24 h, 50 IU/kg (100 IU/dL) for adults and adolescents or 65 IU/kg (130 IU/dL) for children. ^a
Turoctocog alfa pegol (BDT, GlycoPEGylated) 2019 USA	PwHA without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults: OSA, 21.7 h. Adolescents: OSA, 17.4 h. Children (1–12 y): OSA, 13.8–14.7 h.	Adults and adolescents: every 4 days, 50 IU/kg. Children: twice weekly, 65 IU/kg.	Moderate BE: additional dose after 24 h, 40 IU/kg (80 IU/dL) for adults and adolescents or 65 IU/kg (130 IU/dL) for children. ^a Major BE: additional dose(s) every 24 h, 50 IU/kg (100 IU/dL) for adults and adolescents or 65 IU/kg (130 IU/dL) for children. ^a	Major surgery: additional doses every 24 h for the first week; and then, every 48 h, 50 IU/kg (100 IU/dL) for adults and adolescents or 65 IU/kg (130 IU/dL) for children. ^a
Recombinant FIX (SHL)						
Nonacog alfa 1997 USA	PwHB without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults and adolescents: 21.5–23.9 h. Children (2–12 y): 16.3–16.7 h.	Once weekly, 100 IU/kg	Minor, moderate, and major BE: every 12–24 h; 20–30, 25–50, and 50–100 IU/dL, respectively.	Minor and major surgery: every 12–24 h; 25–50, and 50–100 IU/dL, respectively.

			Infants (<2 y): 15.6 h.			
Nonacog gamma 2013 USA	PwHB without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults and adolescents: 25.7 h. Children: 23.2–27.7 h.	Twice weekly. Adults and adolescents: 40–60 IU/kg; children: 60–80 IU/kg.	Minor, moderate, and major BE: every 12–24 h; 20–30, 25–50, and 50–100 IU/dL, respectively.	Minor surgery: every 24 h, 30–60 IU/dL. Major surgery: every 8–24 h, 80–100 IU/dL.
Trenonacog alfa 2015 USA	PwHB without inhibitors; PTPs	Adults and adolescents	24 h.	Twice weekly, 40–70 IU/kg	Minor and moderate BE: every 24 h; 30–60 and 40–60 IU/dL, respectively. Major and life-threatening BE: every 12–24 h, 60–100 IU/dL.	Minor surgery: every 24 h, 30–80 IU/dL. Major surgery: every 8–24 h, 20–80 IU/dL.
Recombinant FIX (EHL)						
Albutrepenacog (albumin fusion protein) 2016 EU	alfa PwHB without inhibitors; PTPs and PUPs	All age groups	Adults: OSA, 95.3 h. Adolescents: OSA, 88.8 h. Children (1–12 y): OSA, 86.2–89.3 h.	Adults and adolescents: once weekly, 35–50 IU/kg; 10 or 14 day intervals, up to 75 IU/kg. Children: once weekly, 35– 50 IU/kg.	Minor and moderate BE: single dose. 30–60 IU/dL. Major BE: repeat every 24– 72 h for the first week; and then, maintenance dose weekly. 60–100 IU/dL.	Minor surgery: single dose, 50–80 IU/dL. Major surgery: every 24–72 h for the first week; and then, 1–2 times per week. 60–100 IU/dL.

Eftrenonacog fusion protein) 2014 USA	alfa (Fc	PwHB without inhibitors; PTPs and PUPs	Adults, adolescents, and children (≥ 1 y)	Adults: OSA, 86–97 h. Adolescents: OSA, 80–94 h. Children (2–10 y): OSA, 68–72 h	Adults and adolescents: once weekly, 50 IU/kg; or once every 10 days, 100 IU/kg. Children: once weekly, 60 IU/kg.	Minor and moderate BE: every 48 h, 30–60 IU/dL. Major BE: every 24 h for the first 3 days; then, every ≥ 48 h. 80–100 IU/dL.	Minor surgery: single dose, 50–80 IU/dL. Major surgery: every 24 h for the first 3 days; and then, every ≥ 48 h, 60–100 IU/dL.
Nonacog (GlycoPEGylated) 2017 USA	beta pegol	PwHB without inhibitors; PTPs and PUPs	Adults, adolescents, and children	Adults: OSA, 83.0 h. Adolescents (13–17 y): OSA, 89.4 h. Children (≤ 12 y): OSA, 69.3–76.3 h.	Once weekly, 40 IU/kg (approved only in the EU)	Minor, moderate, and major BE: single dose; 40, 40, and 80 IU/kg, respectively.	Minor surgery: single dose, 40 IU/kg. Major surgery: pre-operative, single dose, 80 IU/kg. Post-operative: 1–3 day intervals within the first week; then, once weekly, 40 IU/kg.
Antibody							
Concizumab 2023 Canada		PwHB with inhibitors	Adults and adolescents ^d	Single dose: 39–195 h; multiple doses: 38 h.	Once daily; loading dose: 1 mg/kg; maintenance dose: 0.2 mg/kg for 4 weeks; then, 0.15–0.25 mg/kg.	Not applicable	Not applicable

Emicizumab 2017 USA	PwHA with or without inhibitors	All age groups	26.9 days	Once every 1 (1.5 mg/kg), 2 (3.0 mg/kg), or 4 (6.0 mg/kg) weeks Loading dose: 300 mg; Maintenance dose: one week after the loading dose, 150 mg every week on the same day each week. Dose adjustment to 300 mg weekly can be considered.	Not applicable	Not applicable
Marstacimab 2024 USA	PwHA or PwHB without inhibitors	Adults and adolescents	7–10 days		Not applicable	Not applicable
Gene therapy						
Fidanacogene elaparvovec (pdv-FIX) 2024 Canada, USA and EU	PwHB without inhibitors	Adults	Not applicable	For one-time, single-dose, intravenous use only; $5 \times$ 10^{11} vg/kg.	Not applicable	Not applicable
Etranacogene dezaparvovec (pdv-FIX) 2022 USA	PwHB without inhibitors	Adults ^e	Not applicable	For one-time, single-dose, intravenous use only; $2 \times$ 10^{13} gc/kg.	Not applicable	Not applicable

Valoctocogene roxaparvovec (BDD-FVIII) 2022 EU	PwHA without inhibitors	Adults ^f	Not applicable	For one-time, single-dose, intravenous use only; 6 × 10 ¹³ vg/kg.	Not applicable	Not applicable
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23 The information listed in this table was obtained from the product package inserts. Small children (SC), 0 to <6 y; older children (OC), ≥ 6 to < 12 y; adolescents, ≥ 12 to < 18 y;
 24 adults, ≥ 18 y. Abbreviations: OSA, one-stage clotting [activated partial thromboplastin time (APTT)] assay; TSA, two-stage (chromogenic) assay; BE, bleeding episode; PwHA,
 25 patients with hemophilia A; PwHB, patients with hemophilia B; PTP, previously treated patients; PUP, previously untreated patients; SHL, standard half-life; EHL, extended half-
 26 life; FL, full-length; BDD, B-domain deleted; BDT, B-domain truncated. EU, European Union; USA, United States of America; pdv-FIX, FIX-Padua variant; vg, vector genomes;
 27 gc, genome copies.

28 ^a One IU per kg body weight will increase the FVIII level by 2% of normal or 2 IU/dL.

29 ^b One IU per kg body weight will increase the FIX level by 1% of normal or 1 IU/dL.

30 ^c Clinical trials of efanesoctocog alfa did not include sufficient numbers of participants aged ≥65 y to determine whether they responded differently from the younger participants.

31 However, clinical experience with other FVIII products has not revealed differences between older and younger patients.

32 ^d Clinical studies did not include sufficient numbers of patients aged ≥65 y to determine the overall benefit-risk profile of concizumab in these patients.

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- 33 ^e Six geriatric participants with hemophilia B, aged 68–75 y at the time of enrollment, were included in the study. No meaningful differences in the safety and efficacy profile
- 34 were observed in these participants compared to participants aged 18–65 y, and no dose adjustment was made.
- 35 ^f A single patient aged ≥ 65 y was treated with valoctocogene roxaparvovec.