Hemophilia:
Treatment Analysis and Market Evaluation of Hemlibra

Three Student Team

Names Deleted

Introduction

Many hundreds of years ago there were numerous descriptions of how male relatives died from uncontrollable bleeding after suffering physical trauma. When we use the extensive medical knowledge that we have now and look back at these accounts, there is a likely chance that the cause of death was from hemophilia, a type of bleeding disorder that prevents the blood from clotting. The prolonged hemorrhaging from a small injury coupled with no proper solution for stanching would have devastated and impacted the lives of many children and their families.

A description of hemophilia, according to the CDC, is known typically as a rare, inherited bleeding disorder that involves the absence or proper functioning of specific blood clotting factors, factor VIII (8) and factor IX (9), that results in continuous bleeding that can occur within or out the body. Since the genes that regulate factors VIII (8) and IX (9) are carried on the X chromosome, that means women are usually carriers while males are most often the ones that are affected. The two main types of inherited hemophilia are Type A, deficient of factor VIII, and Type B, deficient of factor IX, with Type A being the most common. It is important to note, however, that another bleeding disorder commonly confused with hemophilia is von Willebrand disease, in which patients have either a deficiency or absence of von Willebrand Factor (VWF). VWF is another type of clotting factor that has a role in blood clotting, however,

for the purpose of this paper, we will only be considering hemophilia A/B and the clotting factors VIII and IX.

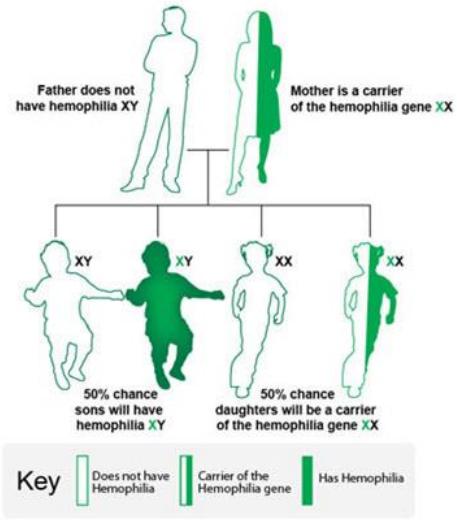

***Figure 1**. Hemophilia is inherited through the X chromosome of the mother who is a carrier and can pass the gene to daughters. (Centers for Disease Control and Prevention, 2020)*

Estimations of the number of males with hemophilia living in the United States are between 30,000 and 33,000 but only 20,000 are receiving prophylaxis, which is a preventative treatment regimen for patients suffering from hemophilia, from federally funded hemophilia treatment centers. Each year, there are about 400 babies that are diagnosed with hemophilia A per year, which is about 1 in 5,000 male births. (J M Soucie, 1998) (Iorio A & Hemophilia., 2019)

To find the total number of males who have hemophilia A, we take the total number of males in the world to be 3.9 billion and the rate of males per 100,000 to be 17.1. We end up with a total of 666,900 males who have hemophilia A with all severities and the rate of males with severe hemophilia A is 6, so the number of males with severe hemophilia A comes out to 234,000. In the case of males with hemophilia B, we take rate of males with hemophilia B to be

3.8 per 100,000 and we get 148,200, for cases of severe hemophilia B, rate being 1.1 per 100,000, we will get 42,900 in the world. (Inserro, 2019)

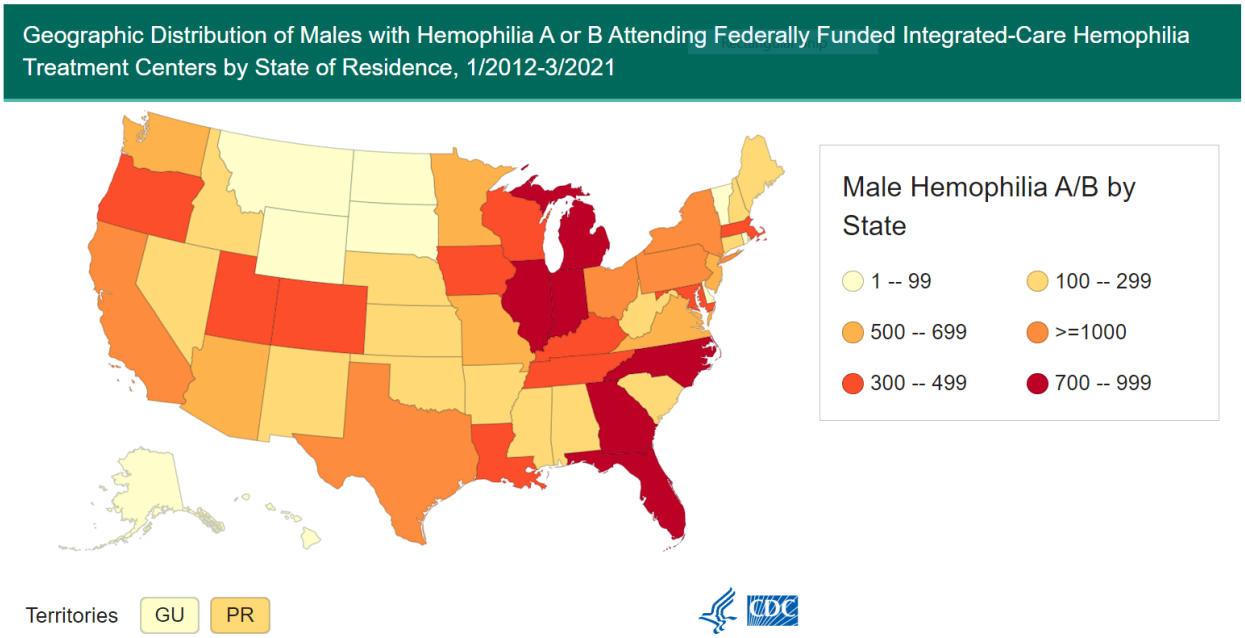

Figure 2. *US distribution of patients with Hemophilia A/B receiving Federal funded care at Hemophilia treatment centers, 01/2012 - 03/2021. (Centers for Disease Control and Prevention, 2020)*

The severity of hemophilia depends on the level of clotting factor is available in a person's blood with the normal range for factor activity being 50-150% (0.5 – 1.5 International Units/mL). Having >5% to <40 (0.05-0.40 IU/mL) factor activity signals mild hemophilia, between 1% and 5% (0.01-0.05 IU/mL) indicates moderate hemophilia, leaving patients with severe hemophilia to have less than 1% (0.01 IU/mL) clotting factor activity in their blood. About 25% of hemophilia patients have a mild form which rarely have bleeding problems but only usually after a trauma. For people with moderate hemophilia, composing of about 15%, they can have cases of spontaneous bleeding without an obvious cause and bleeding will occur after injuries. Having severe hemophilia meant frequent suffering from bleeding and could spontaneously occur into their muscles or joints, posing a critical risk of physical disability. (Cleveland Clinic, 2020) (Indiana Hemophilia & Thrombosis Center, n.d.)

Table 1. *The distribution of Hemophilia A/B in the US based on patient characteristics. (Centers for Disease Control and Prevention, 2020)*

		Hemophilia A (Factor VIII deficiency)(n=21400)										Hemophilia B (Factor IX deficiency)(n=6864)									
		Factor level >=40%		Mild		Moderate		Severe		Severity Unknown		Factor level >=40%		Mild		Moderate		Severe		Severity Unknown	
		#	(%)	#	(%)	#	(%)	#	(%)	#	(%)	#	(%)	#	(%)	#	(%)	#	(%)	#	(%)
	# of patients	1435	(100)	6877	(100)	3455	(100)	9224	(100)	409	(100)	568	(100)	2115	(100)	2383	(100)	1690	(100)	108	(100)
Age (years)	<2	24	(2)	164	(2)	86	(2)	228	(2)	24	(6)	13	(2)	70	(3)	77	(3)	58	(3)	*	*
	2-10	189	(13)	1029	(15)	615	(18)	1718	(19)	64	(16)	106	(19)	315	(15)	450	(19)	320	(19)	19	(18)
	11-19	311	(22)	1556	(23)	728	(21)	1964	(21)	57	(14)	107	(19)	459	(22)	504	(21)	301	(18)	16	(15)
	20-44	574	(40)	2252	(33)	1317	(38)	4112	(45)	169	(41)	244	(43)	663	(31)	766	(32)	677	(40)	35	(32)
	45-64	223	(16)	1155	(17)	483	(14)	971	(11)	67	(16)	66	(12)	386	(18)	377	(16)	257	(15)	21	(19)
	65+	114	(8)	721	(10)	226	(7)	231	(3)	28	(7)	32	(6)	222	(10)	209	(9)	77	(5)	*	*
Sex[†]	Male	245	(17)	5752	(84)	3393	(98)	9180	(100)	162	(40)	89	(16)	1607	(76)	2361	(99)	1683	(100)	57	(53)
	Female	1190	(83)	1125	(16)	62	(2)	44	(0)	247	(60)	479	(84)	508	(24)	22	(1)	7	(0)	51	(47)
Ethnicity	Hispanic, Latino/a, or Spanish origin	215	(15)	1390	(20)	729	(21)	1614	(17)	82	(20)	34	(6)	164	(8)	150	(6)	318	(19)	10	(9)
	Not Hispanic, Latino/a, or Spanish origin	1162	(81)	5361	(78)	2680	(78)	7511	(81)	285	(70)	507	(89)	1910	(90)	2213	(93)	1349	(80)	85	(79)
	Unknown	58	(4)	126	(2)	46	(1)	99	(1)	42	(10)	27	(5)	41	(2)	20	(1)	23	(1)	13	(12)
Race	American Indian/Alaska Native	39	(3)	88	(1)	46	(1)	76	(1)	7	(2)	*	*	*	*	28	(1)	17	(1)	*	*
	Asian	30	(2)	200	(3)	128	(4)	480	(5)	18	(4)	*	*	33	(2)	34	(1)	85	(5)	*	*
	Black or African American	102	(7)	379	(6)	467	(14)	1430	(16)	39	(10)	30	(5)	163	(8)	99	(4)	251	(15)	*	*
	Native Hawaiian or other Pacific Islander	*	*	8	(0)	12	(0)	53	(1)	*	*	*	*	*	*	10	(0)	8	(0)	*	*
	White	1170	(82)	5837	(85)	2662	(77)	6787	(74)	284	(69)	497	(88)	1847	(87)	2165	(91)	1274	(75)	95	(88)
	More than one of these	*	*	98	(1)	38	(1)	148	(2)	*	*	*	*	10	(0)	15	(1)	14	(1)	*	*
	Unknown	79	(6)	267	(4)	102	(3)	250	(3)	55	(13)	27	(5)	54	(3)	32	(1)	41	(2)	7	(6)
Insurance Status	Insured	1368	(95)	6586	(96)	3277	(95)	8819	(96)	350	(86)	423	(74)	1857	(88)	1840	(77)	1619	(96)	77	(71)
	Uninsured	36	(3)	184	(3)	111	(3)	214	(2)	29	(7)	112	(20)	223	(11)	511	(21)	42	(2)	18	(17)
	Unknown	31	(2)	107	(2)	67	(2)	191	(2)	30	(7)	33	(6)	35	(2)	32	(1)	29	(2)	13	(12)
History of HCV infection	Yes	46	(3)	874	(13)	714	(21)	2283	(25)	30	(7)	6	(1)	204	(10)	393	(16)	517	(31)	10	(9)
	No	1083	(75)	5239	(76)	2524	(73)	6467	(70)	233	(57)	392	(69)	1611	(76)	1710	(72)	1074	(64)	57	(53)
	Unknown	306	(21)	764	(11)	217	(6)	474	(5)	146	(36)	170	(30)	300	(14)	280	(12)	99	(6)	41	(38)
History of HIV infection	Yes	11	(1)	107	(2)	186	(5)	934	(10)	12	(3)	*	*	28	(1)	45	(2)	131	(8)	*	*
	No	1123	(78)	5933	(86)	3024	(88)	7739	(84)	251	(61)	398	(70)	1768	(84)	2023	(85)	1439	(85)	62	(57)
	Unknown	301	(21)	837	(12)	245	(7)	551	(6)	146	(36)	*	*	319	(15)	315	(13)	120	(7)	*	*

While there are some even rarer cases where males and females can acquire hemophilia, that has a 1 in a million chance of happening and only shares little similarities with inherited hemophilia because it is considered more as an autoimmune disorder. These patients develop antibodies against blood clotting factors, often Factor VIII, which impairs the blood's ability to clot and trying to identify why production of factor antibodies occurs suddenly remain unknown in about 50% of cases. In the known cases, it may have been associated with illnesses such as rheumatoid arthritis, cancers, or triggered from therapies, or by pregnancy. (Centers for Medicare & Medicaid Services, n.d.) (Hemophilia News Today, 2021)

Historical Treatments for Hemophilia

Back in the early 1900s, average life expectancy for people with hemophilia was just 13 years old and called for frequent blood transfusions which were directly sourced from the family members since there was no way to store the blood. By the 1960s, the introduction of fresh frozen plasma had resulted in only a 7-year increase for patients with severe hemophilia due to the minute quantity of the crucial clotting factor in the treatment.

Although the disorder cannot yet be cured, there have been huge strides in obtaining treatments for its prophylaxis. Early breakthrough treatments for patients with hemophilia started at the beginning of the 20th century and involved a series of blood transfusions to control spontaneous muscle and joint bleeding. Although these transfusions offered some benefit in aiding clotting, there is not enough factor VIII or IX in an original blood transfusion to be a complete and effective solution. In 1901, the U.S. Surgeon General had catalogued the use of lime, inhaled oxygen, thyroid gland hormones, bone marrow, hydrogen peroxide, and gelatin as additional treatments for hemophilia. By the 1930s, it was discovered that certain types of diluted snake venom could cause blood to clot and consequently be used for patients with hemophilia, however the primary method of treatment was still transfusion. Eventually transfusions moved towards primarily being plasma rather than just blood, however the biggest issue with these transfusions was still the low amount of factor VIII and IX in these treatments.

In 1965, Stanford researcher Dr. Judith Graham Pool discovered that cryoprecipitate, which is the precipitate left from thawing plasma, had a much higher concentration of factor VIII in a lower volume of fluid. This cryoprecipitate could be produced by blood banks and used for emergency surgeries to control bleeding. Shortly thereafter, freeze dried powder concentrates containing factors VIII and IX became available for patients and was able to be kept at home for

self-infusions. These plasma-derived factor concentrates were the first majorly effective treatment for patients suffering from hemophilia and were the main treatment option up until the mid-1990s, when synthetic factor concentrates started becoming available.

One of the consequences of using plasma-derived factor concentrates was that there was a possibility of HIV and Hepatitis-C transmission. In 1992, the FDA approved the first synthetically produced recombinant factor VIII concentrate, which did not carry the risk of spreading any blood borne diseases. Soon after in 1997, a recombinant factor IX concentrate was approved by the FDA. During this time, prophylaxis became the wide-spread standard and maintains the levels of clotting factors in patients rather than introducing additional clotting factors for patients already suffering from a bleeding episode. Hemophilia Treatment Centers (HTCs) would be the primary method for maintaining these treatment regimens for patients, and over time would offer additional novel recombinant factor concentrate treatments as the FDA approved them. Plasma-derived factor concentrates became less favorable, and are now rarely or indicated in patients with either hemophilia A or B.

Product

Hemlibra (emicizumab-kxwh), a treatment option for patients with Hemophilia A, is a subcutaneous injection prescribed for preventing or reducing the bleeding episodes of patients of all ages with or without factor VIII inhibitors. The medication can be administered once weekly, once every two weeks, or once every four weeks, depending on how long the medication can remain in a patient's blood at appropriate therapeutic levels. For patients who are starting treatment with Hemlibra, it is recommended that the medication be administered weekly for the first four weeks to bring the levels of the medication to appropriate levels. Once the optimal level of medication in a patient is reached, additional doses can be spaced out and less frequent,

however this depends on the administration schedule determined by the patient's physician. (U.S. Food & Drug Administration, 2018)

Figure 3. *Hemlibra is offered in four dosing vials. (Genentech, n.d.)*

Innovation in Treatment

Hemlibra is an alternative treatment to recombinant factor concentrates, more specifically factor VIII concentrate, which received FDA approval in 1992. Hemlibra is a monoclonal antibody, a laboratory immune system cell made from animal cells without any human plasma or blood, that works by attaching to clotting factors in blood to enable for the proper clotting even without Factor VIII. (Slowiczek, 2019)Existing recombinant factor treatments, such as Advate or Eloctate, had a medication half-life of up to 22 hours, whereas Hemlibra had a half-life of up to 646 hours (about 4 weeks).

In addition, Hemlibra can be administered by yourself after some training at home whereas Advate & Eloctate both require IV which means traveling to the health centers and can be interfering with the daily lives of the patients. Both advantages allow for the users of Hemlibra to have variable treatment schedules that are more flexible to change.

In the STASEY study, one of the largest open studies that assesses the safety and tolerability of a medicine for people with hemophilia A with factor VIII inhibitors, Roche announced in July 2021 that the analysis of Hemlibra from data of 193 patients was consistent with the phase III HAVEN clinical program. The study shown no new safety signals for Hemophilia A patients with inhibitors, both adults and adolescents, who have been taking Hemlibra long term, once weekly for up to 2 years (median treatment duration: 103.1 weeks).

The STASEY study proved that Hemlibra is associated with a low chance of developing anti-drug antibodies, otherwise known as inhibitors and about 1/3 of patients with Hemophilia A develop inhibitors which can require a more intensive treatment schedule as additional complications may arise. Rather than replacing the Factor VIII, it shares the same role by linking other blood proteins and is undetected by the inhibitors. (Slowiczek, 2019) ADA will lessen the efficacy of the treatment, but of those who developed ADAs during the study which were 10 participants, the development of ADA didn't affect the efficacy or safety of Hemlibra. None of them had a decrease in the Hemlibra plasma concentration and none of them experienced a treated bleed, which is a bleed directly followed by a hemophilia medication for treatment of bleeding. In addition to that, the ADAs had disappeared over time when all the participants were tested negative on their last visit. (Roche, 2019) (Roche, 2021)

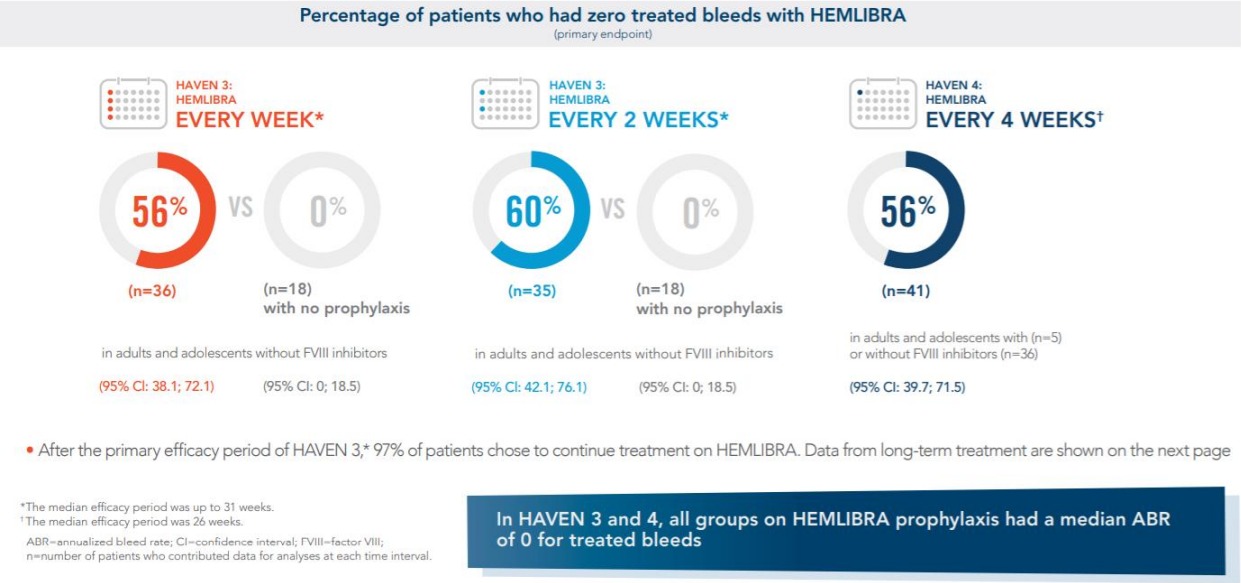

Figure 4. *Results of the HAVEN trials with the primary goal to have zero treated bleeds after initiating Hemlibra. (ajmc)*

Hemlibra continues to demonstrate that it is effective in bleed control with 82.6% of its (Iorio A & Hemophilia., 2019) participants not experiencing any bleeding episodes that required treatment as well as the consistent projection of annual bleeds with previous reported observations from the HAVEN studies. The HAVEN clinical trial program, one of the largest clinical trial programs in hemophilia A, assesses the efficacy and safety of Hemlibra in people with and without factor VIII inhibitors. Its goal is to overcome current clinical challenges which are the short-lasting effects of treatments, development of factor VIII inhibitors and the need for frequent venous access. (National Hemophilia Foundation, n.d.)

FDA Trial Timeline

June 25, 2017: Genentech's Emicizumab provided positive results in their Phase III studies with (HAVEN 1 and HAVEN 2) for Hemophilia A patients with inhibitors.

August 23, 2017: FDA grants a priority review for Genentech's Emicizumab of Hemophilia A with inhibitors.

Approved: November 16, 2017: FDA approves Hemlibra for Hemophilia A with inhibitors.

April 16, 2018: Genentech is given breakthrough therapy designation by FDA for Hemlibra in Hemophilia A without inhibitors

Approved: October 4, 2018: FDA approved Genentech's Hemlibra for patients with Hemophilia A without Factor VIII inhibitors.

(Drugs.com, n.d.)

Orphan Drug Classification and Revenues

The overall patient population of those diagnosed with hemophilia in the United States is extremely small when compared to other well-known diseases, and therefore it can be difficult to incentivize biopharmaceutical companies to research and develop treatments that are able to recover costs. The Orphan Drug Act of 1983 was passed in order to facilitate commercial investment in firms to develop treatments for diseases with small patient populations by providing financial incentives, including seven years of market exclusivity, tax crediting of up to fifty percent for research and development expenses, and exemption from certain user fees. Prior to this legislation, patients suffering from rare diseases were often being left behind by firms in favor of more profitable drug pipelines with larger patient pools, lesser risk, and greater profit margins. The Orphan Drug Act of 1983, designed to address this issue, enabled more firms to pursue development and advance the front on treating these rare diseases, including hemophilia, by granting these treatments an orphan drug classification. It was later specified that a rare disease in the context of the Orphan Drug Act was one that affected less than two hundred thousand individuals in the United States, however a disease with more than two hundred

thousand patients could qualify if a firm could prove their inability to recover costs. (U.S. Food & Drug Administration, n.d.)

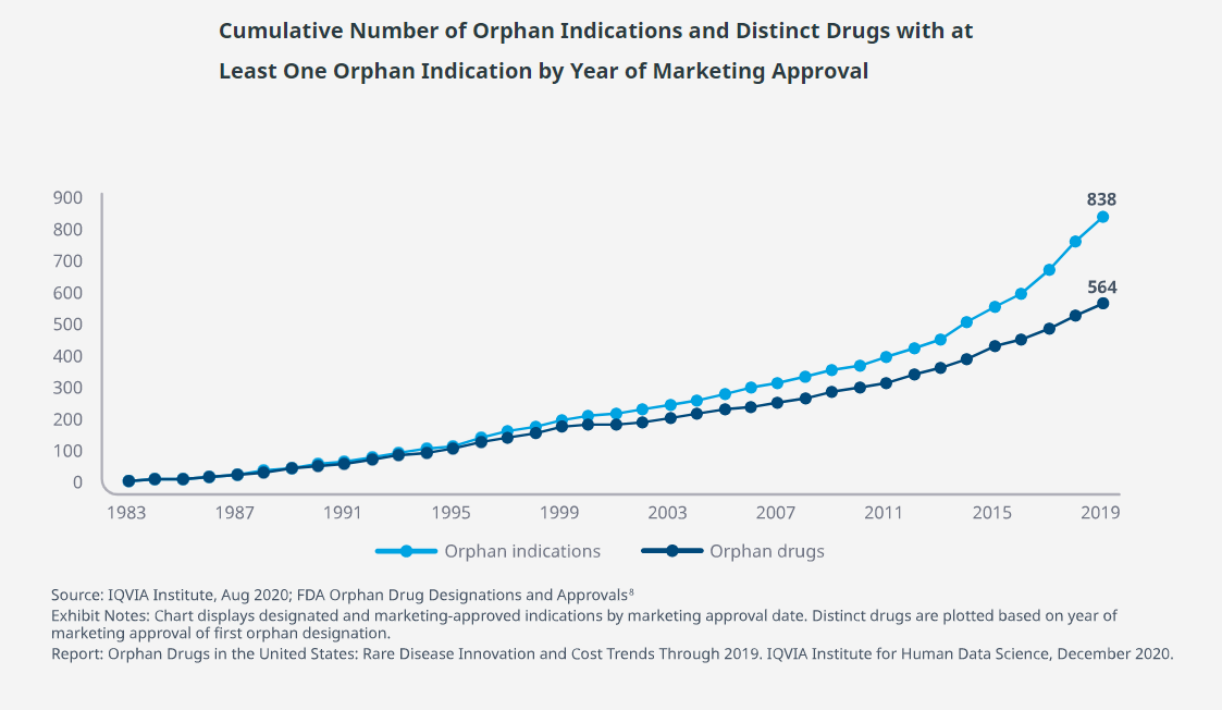

Figure 55. *Comparison of orphan drug indications, which are diseases that classify as rare under the Orphan Drug Act of 1983 and developed orphan drugs (not necessarily approved). (IQVIA Institute, 2020)*

Since 1983, there has been an increased rate at which orphan drugs are being developed, showing greater market force towards developing orphan drugs and bringing them to market. Genentech's Hemlibra received two orphan drug classifications from the FDA, one in 2017 and one in 2018. Roche, the parent company of Genentech, reported $229 million in global sales for 2018 and $1.4 billion in global sales for 2019. It is important to note that Roche saw a huge jump

in sales once Hemlibra was approved for patients with or without inhibitors in October of 2018.

Figure 66. *Roche Holding AG (RHHBY) 07/2016 - 12/2021*

Genentech is a privately held company, therefore there is no public value for an individual share. When examining Roche and its stock values, there is notable growth starting mid-2018 and increasing until now. It should be noted, however, that there are other developments occurring in this period, such as Roche's new Alzheimer's drug, gantenerumab (not yet approved), that are affecting the company's individual stock price, and the growth cannot entirely be attributed to Hemlibra. The growth in sales of Hemlibra has also offset the decline in some of Roche's other products that are facing increasing competition from biosimilars. (BusinessWire, 2021)

Drug Pricing and Insurance Access

Upon approval in 2017, the price of Hemlibra was set to $3226.05 for a milliliter of 30 mg/mL solution. Available doses ranged from 30 mg/mL solutions to 150 mg/mL solutions, each sharing the same price per mg of approximately $107.

30 mg/mL
Hemlibra subcutaneous solution
from $3,226.05
for 1 milliliter(s)

Quantity	Per unit	Price
1 milliliter	$3,226.05	$3,226.05

150 mg/mL
Hemlibra subcutaneous solution
from $16,092.21
for 1 milliliter(s)

Quantity	Per unit	Price
1 milliliter	$16,092.21	$16,092.21

Figure 77. *Hemlibra Price Range for Different Doses (Drugs.com, n.d.)*

Hemlibra can be administered weekly, every two weeks, or every four weeks, but the amount of the drug needed increases linearly with said timespans, making it most efficient to analyze price in terms of weekly doses. The dosage required also depends on the weight of the patient so the average weight of an American adult male will be used (197.6 lbs/89.6 kg) (James, 2021). Finally, the dosage for the first four weeks will be double that of the maintenance doses.

Loading Dose* (Weeks 1-4)	**Maintenance Dose Options*** (Weeks 5+)	
Once weekly (3 mg/kg)	TOTAL DOSE (mg):	Once weekly (1.5 mg/kg)
TOTAL DOSE (mg): **270 mg**		135 mg

Figure 88. *Calculated Weekly Dosage by Weight (Genentech, n.d.)*

Thus, the weekly loading dose price is $29034.45 while the weekly maintenance dose price is $14517.23. Since Hemlibra is not a cure, it needs to be continually taken, resulting in an annual price of $812,964.60 for the first year, then $754,895.70 for subsequent years. This calculation represents the highest cost group of patients as American adult males are typically the

heaviest population category. For more general patient populations, this price will significantly decrease depending on the weight of the patient.

For patients with private insurance, Genentech offers a HEMLIBRA Copay Program to further alleviate the cost of the drug. The program offers up to $15,000 in assistance annually for co-pay, co-insurance, or deductible costs in addition to six months of past costs, resulting in co-pays of as low as $5 per dose (Genentech, n.d.).

Competition for Treatment

Before Hemlibra was introduced into the market, the treatments used for prophylaxis were primarily recombinant factor concentrates, including Advate, released in July of 2003 by Baxter Healthcare Corporation, and Eloctate, released in June of 2014 by Biogen. Advate has a standard medication half-life of about 12 hours while Eloctate has an extended half-life of about 19 hours. Hemlibra, which has a medication half-life of about 646 hours, allows patients to have a much laxer prophylaxis schedule, as compared to patients using either Advate or Eloctate, which require more frequent doses to maintain adequate levels of factor VIII.

In addition, the STACEY trials found that patients taking Hemlibra were less likely to develop inhibitors, and even if they did, the medication still maintained efficacy and effectiveness in controlling bleeding. Recombinant factor VIII concentrate treatments in general have a higher likelihood of developing inhibitors for patients, which significantly increases cost of treatment.

As aforementioned, Hemlibra can be administered subcutaneously at home with a much lower frequency of required dosing. Paired with its novel inhibitor-independent mechanism of action, Hemlibra stands as a more clinically attractive solution for patients with hemophilia.

From 2018 to 2020, sales of Advate more than halved ($2.806 million to $1.213 million), likely due to competition from Genentech's Hemlibra, which is set to achieve market leader in future forecasts. (FDA, 2017)

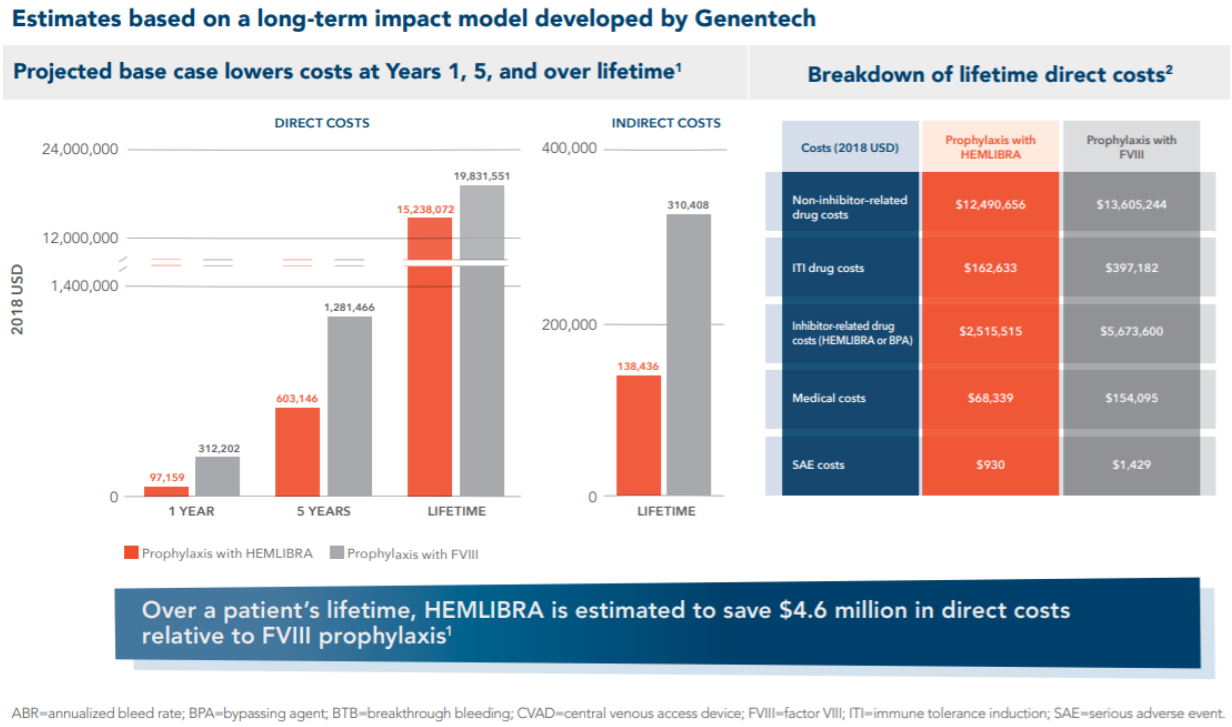

Figure 9. *Projected overall costs of prophylaxis with Hemlibra vs. prophylaxis with factor VIII concentrates over time 9 (ajmc)*

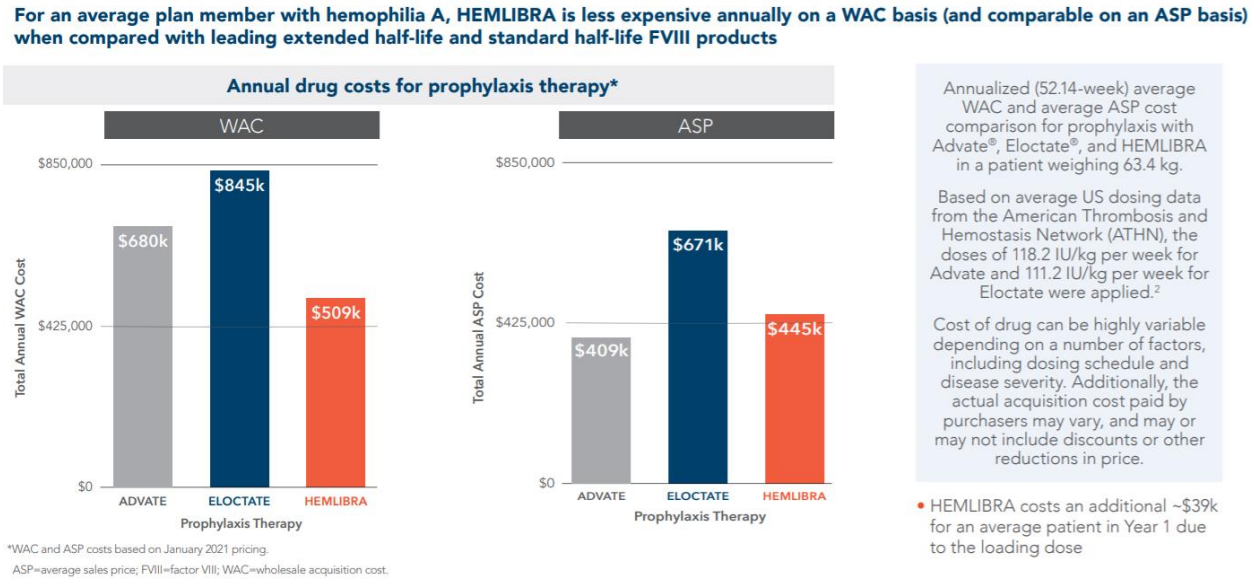

Figure 10. *Annual drug costs comparing Hemlibra with the leading factor VIII concentrate treatments (ajmc)10*

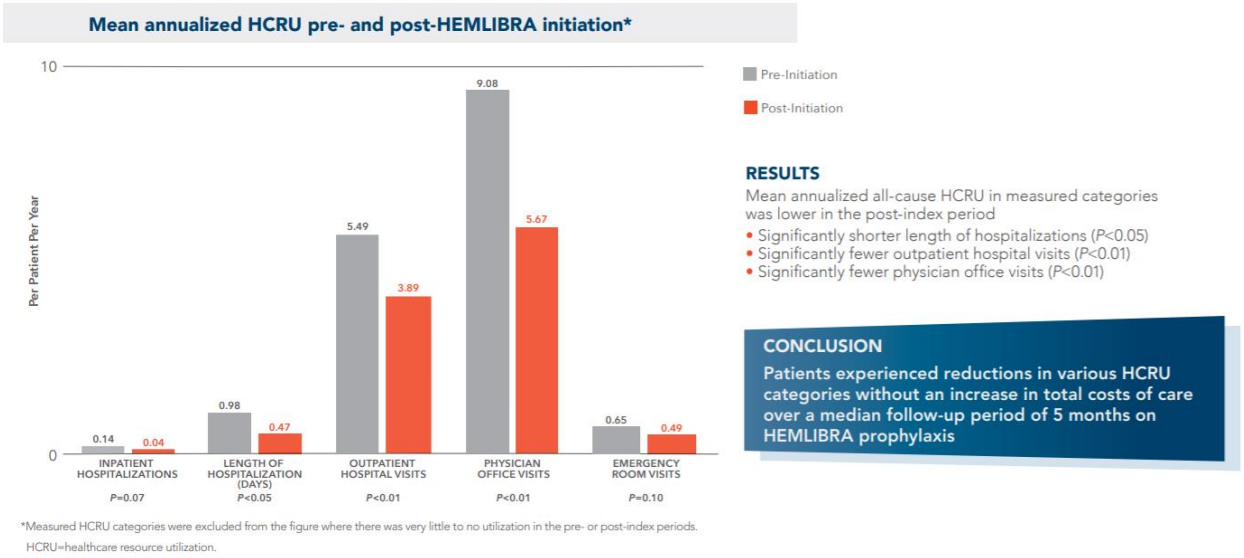

Figure 11. *Post-Hemlibra trials shows a reduction in Healthcare Resource Utilization, significantly lowering the time of patients spent for visits. (ajmc)11*

Costs on the American Healthcare System

Hemlibra users on Medicare receive only Part B benefits, covering treatment related services such as doctors' services, instead of Part D coverage which would include prescription drug costs.

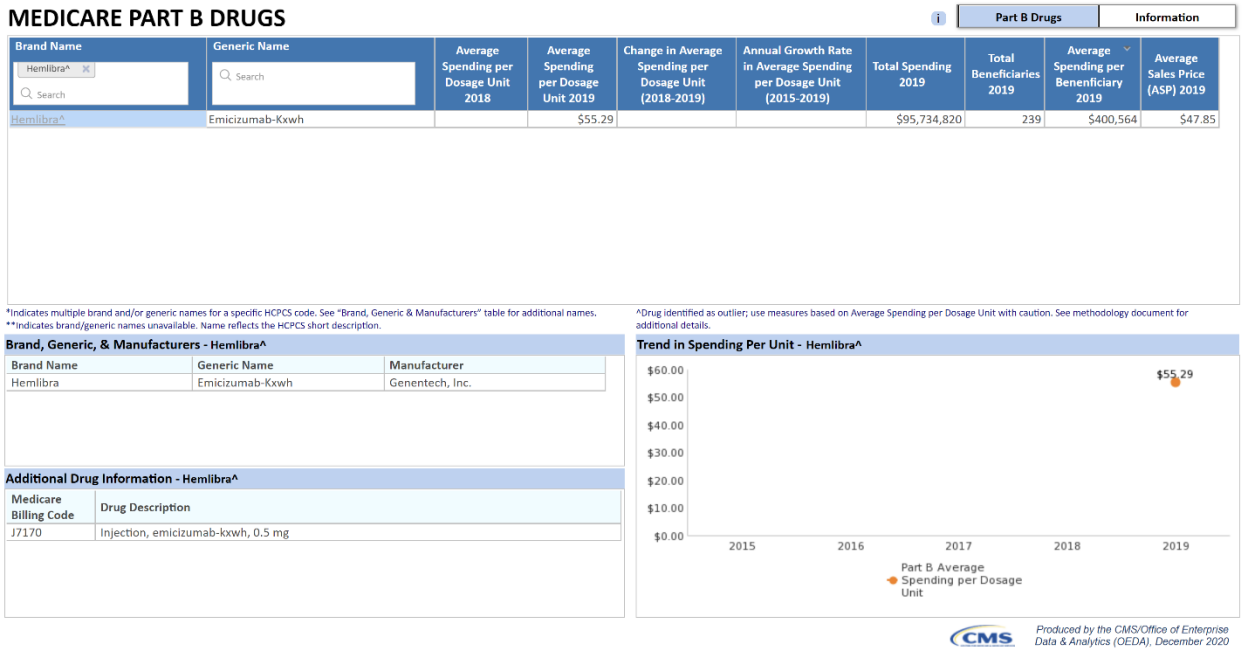

Figure 1212. *Medicare Part B Coverage of Hemlibra (CMS/Office of Enterprise Data & Analytics (OEDA), 2020)*

Instead, the majority of Hemlibra cost relief from publicly funded health care in America is through Medicaid, which covered $10,005.25 per dose on average in 2019.

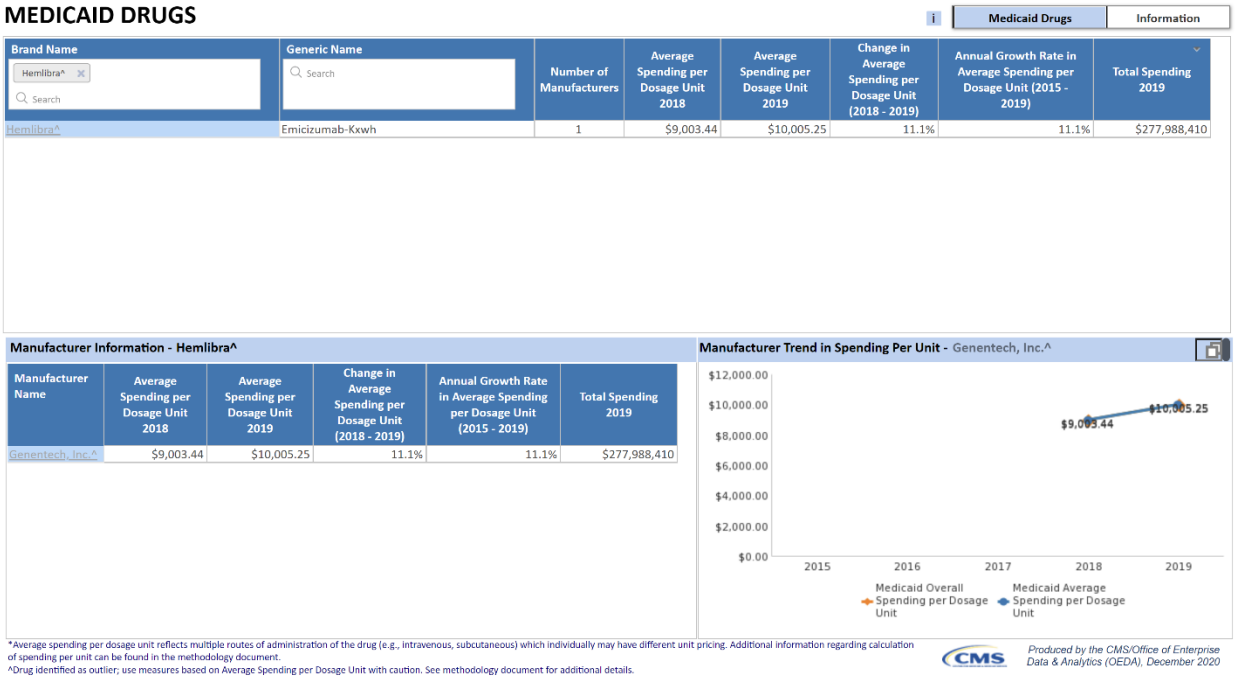

Figure 1313. *Medicaid Coverage of Hemlibra (CMS/Office of Enterprise Data & Analytics (OEDA), 2020)*

Assuming the average American patient needs 100 mg weekly, the sticker price of the drug would be $10,728.14 weekly, while costing $557.863.28 annually. With Medicaid coverage, the weekly cost is reduced to $722.89, resulting in an annual cost of $37,590.28 for the patient and $520,273 in expenditures per patient for Medicaid. From this data, approximately 534 Hemlibra users were covered by Medicaid in 2019.

Global Revenue

Hemlibra was approved for use in hemophilia A patients with inhibitors in November 2017 by the FDA. The following year in February and March, Hemlibra was also approved for use in the EU and Japan for patients with inhibitors, respectively (Chugai Pharmaceutical Co., LTD, 2018). This period represents the initial release of the drug to approximately one-third of

the available hemophilia A populations in three major markets. However, through the end of 2018 the drug would only be available to American and Japanese markets as individual European nations had yet to reach agreements with Roche. This resulted in a relatively low global revenue of $227 million for the five quarters from FDA approval through the end of 2018.

Figure 1414. *Global Hemlibra Sales Since Initial Approval (Loncar, n.d.)*

In October of 2018, the FDA approved the drug for use in non-inhibitor cases of hemophilia A, greatly expanding the accessible market for Hemlibra. With this increased accessibility, the quarterly revenue from Hemlibra nearly doubled for two consecutive quarters, with the first quarter of 2019 generating $217 million - nearly as much revenue as the five since initial launch combined.

Throughout 2019, the adoption of Hemlibra in American and Japanese markets continued to rise, contributing to the growing global sales of the drug. Additionally, European nations were beginning to reach agreements with Roche to distribute Hemlibra. Notably, the United Kingdom's National Health Service announced that it would cover Hemlibra for 2,000 patients, or approximately one-third of its total hemophilia A patient population, in August of 2019

(Sagonowsky, 2019). Roche was estimated to have provided Hemlibra to the U.K. with a quarter discount (Bell, 2019). This expansion of Hemlibra into new markets resulted in a global revenue of $1.424 billion during 2019.

Table 2. *Timeline of Hemlibra Globalization (European Medicines Agency, 2021)*

Event	Date
FDA approves Hemlibra for patients with inhibitors	November 16, 2017
Hemlibra receives marketing authorization in the EU	February 23, 2018
Japan NHI approves manufacturing and marketing of Hemlibra	March 23, 2018
Chugai announces Hemlibra's launch in Japan for patients with inhibitors	May 22, 2018
FDA approves Hemlibra for patients without inhibitors	October 4, 2018
U.K. NHS announces deal with Roche to cover Hemlibra	August 21, 2019

Annual global revenue from Hemlibra is estimated to reach $5 billion in the next few years (Trefis Team, 2020).

Cost Utility

In September 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) published their research on the probabilistic benefits of Hemlibra (emicizumab) as a prophylaxis compared to bypassing agent (BPA) prophylactic and on-demand treatments. In this study, the life expectancies were equalized for each treatment to presumably approximately 70 years upon reviewing other sources (BioNews Incorporated, n.d.). Patients treated with BPA on-demand were also assumed to experience two arthroplasties in their lifetimes (those on prophylaxis experience none), each resulting in an additional disutility of -0.39 for one month.

For Hemlibra, the lifetime QALYs gained was 31.476 while the lifetime cost was 32,574,676 Canadian Dollars (CAD).

Table 33. *Total Cost and QALY Comparisons (CADTH Technology Review, 2019)*

	Emicizumab	BPA Prophylaxis	BPA On-Demand	Incremental Difference (Emicizumab vs. BPA Prophylaxis)	Incremental Difference (Emicizumab vs. BPA On-Demand)
Total costs ($)	32,574,676	88,227,298	19,814,261	–55,652,622	12,760,415
Total QALYs	31.476	24.078	22.496	7.397	8.980
ICUR ($/QALY)				Dominates	1,420,982

Upon evaluating the total costs, total quality-adjusted-life-years (QALY), and incremental cost-utility ratios (ICUR) for each of the three hemophilia treatment methods, the benefits of Hemlibra prophylaxis became apparent. When comparing Hemlibra and BPA prophylaxis, Hemlibra provides 7.397 more QALYs (+30.7%) while costing 55,652,622 CAD less, making it strictly superior as a prophylaxis in terms of cost utility. When compared to BPA on-demand, Hemlibra also provides a significant increase in QALYs (+39.9%) but with an additional cost of 12,760,415 CAD, resulting in an ICUR of 1,420,982 CAD.

Generally, one QALY is valued at 50,000-150,000 USD which is significantly lower than the ICUR from Hemlibra when compared to on-demand BPA (Smith, 2019). However, the cost per QALY for each treatment method also greatly exceed the consensus value for a QALY.

Table 4. *Monetary Values of QALY by Drug*

	Emicizumab	BPA Prophylaxis	BPA On-Demand
Cost per QALY (CAD/QALY)	1,034,905.20	3,664,228.67	880,790.41

Thus, in the context of hemophilia treatments, the perceived value of a QALY is specific to each patient. Hemlibra is a significant breakthrough compared to conventional hemophilia treatments, providing a 39.9% increase in total QALYs for a 17.5% increase in price per QALY.

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