Canadian Hemophilia Society
Help Stop the Bleeding
Société canadienne de l'hémophilie
Arrêtons l'hémorragie

Submission to Canadian Blood Services regarding access to Hemlibra for people with hemophilia A without inhibitors to factor VIII

Name of group	**Canadian Hemophilia Society (CHS)**
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Type of group	**Not-for-profit charity representing people with bleeding disorders (patient association)**

January 21, 2021

HISTORY

Founded in 1953, the Canadian Hemophilia Society (CHS) is a national voluntary health charity. Its mission is to improve the health and quality of life of all people in Canada with inherited bleeding disorders and ultimately find cures. Its vision is a world free from the pain and suffering of inherited bleeding disorders.

The Canadian Hemophilia Society, whose **national headquarters** are in Montreal, is an organization that works at three levels: nationally, provincially and locally. We have **ten provincial chapters** across the country.

Its **Board of Directors** is made up of 16 individuals with valuable skills and representing the organization's 10 provincial chapters. Each provincial chapter in turn is managed by its own Board of Directors. Many chapters are separately incorporated and have their own charitable registrations. Three provinces—Quebec, Ontario and Manitoba—currently have offices with permanent staff. The national organization and its chapters share a common vision and mission. The CHS has approximately 300 active volunteers across the country, including people affected by bleeding disorders, family members, friends and health care providers who work in the bleeding disorder treatment centres.

The CHS is affiliated with the World Federation of Hemophilia (WFH) and its more than 140 National Member Organizations around the world; the WFH is officially recognized by the World Health Organization. We work in collaboration with the health care providers in Canada's 26 inherited bleeding disorder comprehensive care centres, whose physicians make up the Association of Hemophilia Clinic Directors of Canada, the blood system operators (Canadian Blood Services and Héma-Québec), the Network of Rare Blood Disorder Organizations, the Canadian Organization for Rare Diseases, the hepatitis C community, the AIDS community and others who share our common interests.

Through the National Corporate Giving Program, the CHS receives funding from a number of pharmaceutical companies that are present in the Canadian market for coagulation therapies. These include Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi and Takeda. None of these companies was involved in the preparation of this submission nor did any contribute funding to support it.

The CHS has policies that govern our relations with companies in the pharmaceutical industry with the goals of …

- maintaining the independence of our organization in representing the needs of people with bleeding disorders;
- being open and transparent with our members, our sponsors, other stakeholders and with the public;
- publicly recognizing the contributions of our sponsors to the bleeding disorder community;
- treating all our sponsors fairly.

Charitable Registration: 11883 3094 RR 0001

Website: **www.hemophilia.ca**

QUESTIONS FROM CBS

1. *Did you or your group receive feedback or input from an individual or group in preparing your submission?* **YES**

2. *If yes, please share who you worked in collaboration with and how you were supported?*

The CHS has gathered information on benefits and risks of Hemlibra and on the patient perspective in a number of ways.

Hemlibra has been in use around the world (in clinical trials via compassionate access and as an approved therapy) since 2016 for patients both with and without inhibitors to factor VIII (FVIII). As of January 2021, over 7,000 patients are reported to be receiving Hemlibra on a prophylactic regimen. Over the last four years, representatives of the CHS have had the opportunity to attend medical symposia around the world and hear about the benefits and risks of Hemlibra first-hand from researchers, clinicians, patients and their caregivers.

Approximately 80 Canadians with hemophilia A and inhibitors to FVIII have been receiving the therapy since May 2019, most of which have FVIII inhibitors. A group of 15 Canadian hemophilia A patients without inhibitors have been receiving Hemlibra via compassionate access since autumn 2019. The CHS has heard about the experiences of these Canadians, either at conferences or in personal meetings, and their experience is reported on pages 5-6 and 7.

The CHS is in regular contact with its members through chapter meetings where current and future therapies are often discussed. From May 23 to 26, 2019, the CHS organized *Rendez-vous 2019*, a conference that assembled the Canadian bleeding disorder community, including people with hemophilia, their caregivers, physicians and allied health care providers. A full-day symposium entitled "The dawn of a new era" was devoted to the evolution of therapies for bleeding disorders, including Hemlibra. Many members of the CHS attended the World Summit of the WFH, held virtually from June 14-19, 2020. Sessions presented the latest research on coagulation therapies, including Hemlibra. Members of the CHS Blood Safety and Supply Committee, which advises the CHS Board of Directors, regularly attend conferences and webinars that feature emerging therapies.

To collect specific perspectives from patients and caregivers with hemophilia A on the burden of disease and treatment, satisfaction with current treatment and the improvements people would like to see in a new treatment, the CHS conducted an online survey between May 31 and June 15, 2019. The survey was publicized via different CHS and chapter communication tools, including the CHS website, e-mail, Facebook, Twitter and Instagram. The questions asked were identical to those in the CADTH patient input template. We received 52 responses from six provinces. All respondents are affected by hemophilia A without inhibitors, 45 with severe hemophilia, four (4) with moderate, two (2) with mild and one (1) unknown severity. The results of that survey are presented in the section on the impact of the CADTH recommendations.

In addition, the CHS collaborated in a Canadian study of 20 patients/caregivers with hemophilia A entitled "From the voices of people with haemophilia A and their caregivers: Challenges with current treatment, their impact on quality of life and desired improvements in future therapies" (Wiley R et al, Haemophilia, **https://doi.org/10.1111/hae.13754**.). The conclusions of that published study are reinforced by our most recent survey data.

3. *Do you consent for your submission to be shared on Canadian Blood Services' website (blood.ca) and with the Provincial and Territorial governments?* **YES**

4. *Did you receive any financial payment from companies or organizations that may have direct or indirect interest in the product under review?* **YES, BUT NOT TO COMPLETE THIS SUBMISSION**

5. *If yes, please provide details including, but not limited to, the amount of financial support/payment and when this was received.*

The CHS receives financial support from a number of companies that supply coagulation products for the treatment of hemophilia A, including Roche.

COMPANY	*Check appropriate dollar range*			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer (manufacturer of rFVIII)				X
CSL Behring (manufacturer of FVIII/VWF, rFVIII, rFIX)				X
Octapharma (manufacturer of rFVIII)				X
Novo Nordisk (manufacturer of rFVIIa, rFVIII, rFIX)				X
Pfizer (manufacturer of rFVIII, rFIX)				X
Roche (manufacturer of Hemlibra)				X
Sanofi (manufacturer of rFVIII, rFIX)				X
Takeda (manufacturer of rFVIII, rFIX)				X

Contact names and information for potential follow-up questions:

David Page, dpage@hemophilia.ca

Deborah Franz Currie, CHS Executive Director, dcurrie@hemophilia.ca

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this stakeholder group in a real, potential, or perceived conflict of interest situation.

Name: David Page

Position: National Director of Health Policy

Stakeholder group: Canadian Hemophilia Society

Date: January 21, 2021

IMPACT OF THE CADTH RECOMMENDATIONS

1. *What would be the impact of listing the product currently under assessment on you or members of your group?*

According to our understanding of the medical literature and patient outcomes reported by people in Canada with hemophilia A without inhibitors (including those receiving FVIII prophylaxis and those receiving Hemlibra via compassionate access) and by people around the world, the introduction of Hemlibra for patients with severe hemophilia A without inhibitors would lead to 1) improved adherence to prescribed treatment, 2) better prevention of bleeding and 3) improved quality of life.

Treatment and adherence impact

- Longer lasting treatment (significantly longer half-life)
- Better protection from bleeding (steady-state bleed protection, higher trough level)
- Less long-term joint damage
- Less frequent administration (once a week or less vs. 2-7 times per week)
- Subcutaneous injection vs intravenous infusion (easier mode of delivery, increased treatment adherence, leading to improved outcomes)
- Reduction in non-drug health care costs (hospital admissions, clinic and emergency department visits, medical tests, professional fees, corrective joint surgeries)

Improved quality of life

- Reduced mental health issues, including stress, anxiety and depression
- Capacity to be more active
- Less dependence on health services
- Less damage to veins from IV infusions
- Fewer visits to clinic, emergency department
- Less time needed to treat
- Less time lost from school, work
- Capacity to contribute more to society
- Less burden on caregivers
- Less impact on siblings
- Improved family quality of life
- Less acute and chronic pain

Comments from non-inhibitor patients and caregivers, and their health care providers, receiving Hemlibra in Canada (via compassionate access)

"The patient and his partner both benefit. They are able to exercise together. They both enjoy the freedom of not planning the day around an infusion. Life feels less stressful, hemophilia is not the focus day to day."

"He is happy to have central line removed and is not worried about needles. He has had less contact and intervention with the health care team and psychologist."

"Parents feel less vulnerable, more empowered and in control. Fewer hospital visits."

"He has more independence. His port will be removed."

"He is now self-injecting, not experiencing stress. He has better self-esteem."

"He has better quality of life with less pain, less focus on acute bleeds and better mobility. Before Hemlibra, the bleeds were a major factor in his life. He is planning on taking on-line IT courses in the fall."

"He is more cooperative. Parents are less anxious, making fewer calls to clinic."

"Quality of life greatly improved! Less joint pain and discomfort. Line flushes are less traumatic."

"The mother was told by the teacher and social worker that he is now a different child. He is not anxious anymore and not having panic attacks with every injury, as in the past."

"There is less family conflict. The patient is more confident, less anxious, and more independent. The family dynamics are better."

"This has been a huge blessing in their lives and has totally changed the way they live now as a family. Hemlibra has allowed them to get the constant burden of hemophilia off their backs and put hemophilia in the background of their family life."

"The patient and the family were apprehensive about stopping factor VIII, but are now seeing benefit."

"I'm finally free and discovering spontaneity in life. After having the sword of Damocles hanging over my head since birth, it's a tremendous relief to be able to embark on an activity without having to think about whether I should inject myself beforehand.

What a surprise. The other day, I hit my elbow hard and didn't do anything to prevent bleeding except trying to rub the pain away. Amazingly, there was no hemorrhage the next day. Hemlibra had protected me without me realizing it!

***INCREDIBLY,** I'm finally free from the yoke of needles and hardened veins after 32 years of prophylaxis. It's unpleasant to give yourself intravenous injections. As for **catheters**, they're very difficult to put in, **painful and uncomfortable**, even for a tough veteran like me."*

"Along with severe hemophilia A, my son suffers from autism spectrum disorder and severe global developmental delay. From the time Vaughn was 10 months old, he was receiving recombinant FVIII product through a port-a-cath. By two years old, he was on infusions every second day. Despite being on the highest recommended frequency of infusions, he experienced frequent joint bleeds in his right knee, along with extensive bruising, frequent alarming goose eggs on his head, a number of mouth bleeds, and two injuries to his port-a-cath. I would guess that he had roughly 100 ER visits in the first 4 years of his life, despite being on home treatments.

My son began showing signs of severe anxiety at any time of injury or needing an infusion. His prophylactic infusions became absolute nightmares, and there were times in which he would end up with worse joint bleeds and bruises simply from being restrained in order to get factor into him. This peaked in October 2019, at which point he had to be sedated in an ER simply to get an infusion into him, as the entire HTC team and my family were unable to keep him calm and still enough to get a poke in safely. He suffered from chronic pain in his knees and would often hide injuries from us to avoid getting treatments.

His mental health was terrible. He was sad or angry most of the time, his severe panic attacks became common at even the slightest injury, was not able to sleep appropriately, and he was not hitting developmental milestones. He was placed in an intensive support pre-school program with a one-on-one educational assistant but had frequent absences due to

injuries and anxiety. We tried counselling, occupational therapy, and every strategy in the book and nothing helped lessen his problems.

It was then that the HTC team suggested applying for the compassionate care program through Roche in order to try Hemlibra. We heard back very quickly that he had been approved, and in January 2020 he started on the product. His injections are only every 2 weeks, plus a monthly port flush. In the 6 months since starting on it, he has had zero bleeds and has only once required factor for a mild concussion. We have had only 1 ER visit, require very minimal support from our HTC team, and are able to completely manage the injections on our own from home. However, the most substantial improvements we've seen have been to his mental health and development.

Since the initial period on Hemlibra, my son has become active, learning to run, jump, and climb like other 4-year-olds. He has become extremely social and his anxiety is limited to only a brief period around his treatments and is much more easily de-escalated. He tells us that he is not in pain anymore, and he enjoys playing with his friends and his sister. His time is no longer spent crying and fighting, he is instead taking up new hobbies and learning new things. He still fights during his treatments but is starting to openly discuss his hemophilia and the necessary treatments without experiencing extreme anxiety just at the thought of it. In the past six months, he was able to catch up on almost every developmental milestone and is now exceeding his age level in several areas. His anger towards his family has completed dissolved since we're no longer forced to restrain and poke him every second day, so we have been able to build strong relationships with him and see how beneficial this has been to him. Last year, we would spend every other day with a 2- to 4-hour anxiety attack, and every night with a sleepless child struggling with chronic pain. We now spend our days just as any other family does. Vaughn was even able to enjoy his first ever camping trip this year, which is something that we would not have been able to try before he was on Hemlibra. We're looking forward to September when he starts kindergarten, as he'll be able to apply his new skills and developments in the classroom and building social skills and try new things without constant pain and anxiety.

You have the power to change lives with access to Hemlibra—the lives of people with hemophilia and the lives of all the families—brothers, sisters, fathers, mothers and even grandparents."

Impact on other products

Patients treated with Hemlibra require very little FVIII for breakthrough bleeding. In clinical studies and real-world observation, annual bleed rates requiring FVIII are below one (1). FVIII is often not needed in minor surgical situations (dental, port removal …).

Additional supports

Training to inject Hemlibra subcutaneously is simple compared to IV infusion. Ancillary products are supplied with the injection kits. The support of bleeding disorder treatment centres remains critical to monitor treatment and measure long-term outcomes.

2. *What would be the impact of not listing the product that is being assessed on you or members of your group?*

Canada would remain one of only two developed countries we know of (along with New Zealand) that does not provide regular access to Hemlibra for its non-inhibitor severe hemophilia A population. Health authorities in the U.K., U.S., Australia, Japan, Ireland, France and many other European countries have recognized the benefits and introduced Hemlibra since its regulatory approval in 2018. Holding back introduction in Canada would have impacts on both treatment outcomes and quality of life. The patient community and the hemophilia health care provider group would be extremely critical of such a decision.

Treatment

Continuation of FVIII prophylaxis means:

- More frequent treatments (2 to 7 times per week vs. 1 per week or less)
- Need for venous access
- Long-term damage to veins from IV infusions
- Need for central venous access devices in children
- Less adherence, poorer outcomes
- More bleeding
- More long-term joint damage and need for corrective joint surgery
- More need for downstream medical services

Quality of life

Not introducing Hemlibra would mean:

- Continued mental health issues including stress, anxiety and depression in a significant proportion of the affected population
- Less capacity to be more active
- More dependence on health services (visits to hemophilia clinic, emergency departments)
- More time needed to treat
- More time lost from school and work
- Less capacity to contribute to society for both patients and caregivers
- More burden on caregivers
- Negative impact on siblings
- Poorer family quality of life
- More acute and chronic pain

Comments from non-inhibitor patients and caregivers who responded to the CHS survey

"I have to give my son a needle every second day. This is time consuming and sometimes very difficult to get/keep a vein. Sometimes multiple needles need to be given. I am always worried I am destroying his veins. Sometimes he resists getting his needle. We always have to be mindful of when his last medicine was given every time he is participating in active play at school or with friends, every time he has a new unexplained pain and whenever he has an injury/accident. He has been prevented from participating in activities (school and social events) on occasion just because he is due his medicine but there is no time to give it to him normally due to my employment. He's missed school and has had to miss/opt out of his extracurricular activities due to bleeds that require he immobilize the body part bleeding."

"We had been treating our son through vein access three times a week but his veins were extremely difficult to find and it was taking 4-6 pokes each time to find a vein and do his treatment. It was also difficult as we were commuting to the hospital at least three times a week for his treatments and he had numerous casts and joint bleeds over two years. So our son had a port insertion last July that failed (an artery was punctured) and had another in November that was successful. This was a traumatic surgery for him and the adjustment to the port was very difficult. Since January, he has been getting treated four times a week through his port. His gripper is put in once a week and then left in for the rest of the week for his other three treatments. This has meant though that for most of the week, he cannot have a bath, or go swimming. It wasn't until the end of March that we have been able to transition to treatments at home. He did still have a bad ankle joint bleed at the end of April and has had to go to the hospital for this a number of times."

3. *CADTH recommends this product be listed with criteria. If implemented, how will these criteria impact you or members of your group?*

CADTH recommends access for patients with severe hemophilia A (intrinsic FVIII level < 1%) who are candidates for routine prophylaxis. The CHS is in general agreement with these criteria. A very small group that is missed by these criteria is those people with moderate hemophilia A (intrinsic FVIII level 1-5%) who have a severe clinical bleeding phenotype and who require prophylaxis similarly to those at less than 1%. Decisions on the need for prophylaxis are a regular part of the clinical management process and not a challenge for clinicians who work in bleeding disorder treatment centres. The CHS agrees that access for patients with mild and moderate hemophilia should await the results of more research.

4. *Do you consider the CADTH recommendation to be consistent with the current standard of care? If not, please explain.*

Yes, the CADTH recommendation is consistent with Principle 8 in the World Federation of Hemophilia Guidelines for the Management of Hemophilia, 3rd Edition, published in July 2020. "The standard of care for all patients with severe hemophilia is regular replacement therapy (prophylaxis) with CFCs (clotting factor concentrates), or other hemostasis products to prevent bleeding, started early in life (before age 3) to prevent musculoskeletal complications from recurrent joint and muscle bleeds." Recommendation 6.5.1 states: "For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with Hemlibra will prevent hemarthrosis, spontaneous, and breakthrough bleeding."

5. *Is there any additional information you would like to share?*

Additional research, initiation conditions

The medical literature clearly shows a reduction in frequency of episodes of joint and muscle bleeding with Hemlibra compared to traditional FVIII prophylaxis. This is due to 1) the mode of action of Hemlibra which allows a constant level of the FVIII mimetic as opposed to the peak-and-trough cycles of FVIII, and 2) the much easier subcutaneous injection once every one, two or four weeks compared to infusion of FVIII via peripheral IV infusions or implanted venous

access devices two to seven times per week. This greatly facilitates improved adherence. Both research and real-world experience show that adherence to Hemlibra is far easier than adherence to FVIII. Better adherence results in superior efficacy and improved outcomes.

30% reduction in non-treatment direct health costs

A study from the Institute of Governance and Policy Analysis, University of Canberra, Australia, concluded that the introduction of emicizumab would result in 30.7% reduction in non-treatment direct costs (AUD$3.771M) to the health care system (hospitalization, professional fees, medical tests, medications, disability supports and alternative treatments) and 19.1% reduction in indirect costs (AUD$2.732M) to patients/caregivers (lost wages, productivity and transport). (The societal burden of haemophilia A. III – The potential impact of emicizumab on costs of haemophilia A in Australia. Brown LJ. Et al. Haemophilia. 2020;26[Suppl. 5]:21–29.)

FVIII prophylaxis does not fully protect against joint damage

In severe hemophilia A, early initiation of prophylaxis provides continued protection against joint damage throughout childhood compared with delayed initiation, but early prophylaxis is not sufficient to fully prevent damage. At the exit of the landmark Joint Outcome Continuation Study, MRI osteochondral damage was found in 77% of those on secondary prophylaxis and 35% of those on primary prophylaxis. (Beth Boulden Warren, Marilyn J. Manco-Johnson et al. **https://doi.org/10.1182/bloodadvances.2019001311**, Blood Adv (2020) 4 (11): 2451–2459.)

Low annual bleeding rate with Hemlibra

The phase III Haven 3 trial showed a low bleeding rate of 1.5 (95% confidence interval [CI], 0.9 to 2.5) with once-weekly injection and 1.3 (95% CI, 0.8 to 2.3) with once-every-two-weeks injection in 152 participants (Mahlangu J et al. NEJM 379;9 nejm.org August 30, 2018).

Lower annual bleeding rate compared to FVIII prophylaxis

The same study reported an intraindividual comparison of 48 patients between Hemlibra and FVIII prophylaxis. In effect, patients were their own controls. The annualized bleeding rate was 1.5 events (95% CI, 1.0 to 2.3) with once-weekly Hemlibra therapy, as compared with 4.8 events (95% CI, 3.2 to 7.1) during FVIII prophylaxis, a 68% lower rate in favor of Hemlibra prophylaxis (rate ratio, 0.32; 95% CI, 0.20 to 0.51; P<0.001). Even in those patients who administered 80% of the prescribed doses of FVIII (a measure of good adherence), the annual bleed rate was 4.3. (Mahlangu J et al. NEJM 379;9 nejm.org August 30, 2018).

Annual bleed rate in Canadian severe hemophilia A patients

The annual bleed rate for FVIII prophylaxis in the HAVEN 3 study is very similar to real-world Canadian evidence from the PROBE study (probestudy.org). Between July 2019 and May 2020, 179 Canadian patients with severe hemophilia A without inhibitors on regular FVIII prophylaxis reported an annualized bleed rate of 4.8. Only 33% of the 159 patients reported 0 or 1 bleed in the preceding year, compared to 55% of the 152 subjects receiving Hemlibra in HAVEN 3. (Raw data is available on request.)

Real-world evidence of very low bleeding rate in children

Data reported by three North American centres in 2020 on 93 pediatric patients with severe hemophilia A (19 with an active inhibitor), median age of 8.6 years, showed an annual bleeding rate that dropped from 4.4 (inhibitors) and 1.6 (non-inhibitors) to 0.4 (both groups) after switching to Hemlibra (P=.0012 and .0025, respectively). Furthermore 89% of children on Hemlibra reported no bleeds. There were 28 minor (this included 21 port removals as these

were no longer needed as the children were no longer receiving intravenous factor replacement) and two major surgical procedures. Three patients received 1-2 doses of factor postoperatively to treat minor bleeding events. No patient discontinued therapy with Hemlibra. (McCary I et al. Haemophilia. 2020;00:1–6.)

Low treated annualized bleed rate in adults with once-monthly injection

The HAVEN 4 study of 48 adult patients (40 of 48 without inhibitors), 41 of whom with target joints, receiving Hemlibra once-monthly, reported an annualized treated bleed rate of 2.4. Only 26% of treated bleeds were spontaneous, showing efficacy in protection from spontaneous bleeding. Eighty-five percent (85%) of the participants reported zero joint bleeds despite pre-existing target joints. (Pipe S et al. Lancet Haematol 2019; 6: e295–305.)

Older Canadian patients have high ABR despite FVIII prophylaxis

This Canadian study reveals that a significant number of older Canadians with severe hemophilia A use FVIII prophylaxis with annual consumption of 3,347 IUs/kg per patient per year, or approximately 250,000 IUs per patient per year. Despite FVIII prophylaxis, their annual bleeding rate remains high at 12, likely due to high susceptibility to joint bleeding from hemophilic arthropathy and limited protection afforded by low FVIII troughs. The low ABR observed with Hemlibra therefore represents an opportunity to significantly reduce morbidity. (Jackson S et al. BMCHematology (2015) 15:4 DOI 10.1186/s12878-015-0022-8.)

Patients prefer Hemlibra over FVIII prophylaxis

A study of patients in HAVEN 3 and HAVEN 4 revealed 99% (75/76) of patients preferred Hemlibra over their previous FVIII prophylaxis. They cited lower treatment frequency, easier administration and less worry about breakthrough bleeds as the reasons for their preferences. (Jiminez-Juste V et al. Poster at ASH AGM, 2018.)

Improved physical health scores and reduced absenteeism with Hemlibra

An analysis of data from HAVEN 3 and HAVEN 4 demonstrated clinically meaningful improvements in physical health scores as measured by Haem-A-QoL: 38.8 at baseline to 27.7 at week 73 and 47.0 at baseline to 26.4 at week 61 for patients in HAVEN 3 and HAVEN 4 respectively (lower scores imply better quality of life). Additionally, the percentage of people who missed no workdays in the previous month increased from 76% pre-Hemlibra to 91% at week 74, and from 79% pre-Hemlibra to 100% at week 61 in patients in HAVEN 3 and HAVEN 4 respectively. (Skinner et al. Poster at the ISTH Congress, 2019.)

Efficacy demonstrated across 400 patients

The four clinical trials in Hemlibra—HAVEN 1, 2, 3 and 4—show excellent efficacy data in 400 patients, with an annualized bleed rate of 1.5 (95% CI, 1.20–1.84) over 83 weeks and a joint ABR 1.0 (95% CI, 0.8–1.3), regardless of age, dosing regimen or inhibitor status. (Callaghan C et al. **http://bit.ly/2X6FE9I**)

Patient reported outcomes from the PROBE study (See probestudy.org)

These data were collected via the online PROBE study between July 2019 and June 2020. A total of 181 Canadian boys and men, aged 11 and older, with severe hemophilia A completed the questionnaire. This represents approximately 20 percent of the Canadian population. Eighty-nine percent (161/181, 89%) were receiving regular prophylaxis (52 weeks a year), five percent (10/181, 5%) were receiving intermittent prophylaxis (less than 45 weeks per year), and five percent (10/181, 5%) were receiving on-demand treatment. The results can be compared to

107 age-matched controls recruited from the general public. They show the considerable burden of disease and impact on daily living of severe hemophilia A across all age groups, despite the current widespread access to and use of modern prophylactic treatment with FVIII.

	Severe hemophilia A		Controls	
Use of mobility devices in the last 12 months (all ages)	51/181	28%	7/107	7%
Difficulties with activities of daily living currently (all ages)	51/181	28%	13/107	13%
Use of pain medication in the last 12 months	128/181	71%	53/107	49%
Reduced range of motion in at least one joint	142/181	78%	N/A	N/A
Working full-time or part-time (22 to 64 years of age)	98/151	68%	70/87	80%
Retired, unemployed or on long-term sick leave (22 to 64 years of age)	40/151	26%	11/87	13%

Access to Hemlibra

This chart shows access to Hemlibra in some countries CHS surveyed.

Country	Reimbursed for non-inhibitor patients	Date of decision	Access criteria	Restrictions (e.g. age)	Reporting
United Kingdom	Yes	August 1, 2019	Severe hemophilia A	None	Patients must report data on Haemtrack (similar to CBDR in Canada)
France	Yes	March 11, 2020	Severe hemophilia A	None	Change in prescription reported to national registry (France Coag)
Ireland	Yes	December, 2019	Severe hemophilia A	None	Reporting via home treatment app

Country	Reimbursed for non-inhibitor patients	Date of decision	Access criteria	Restrictions (e.g. age)	Reporting
Germany	Yes	February 2019	Severe hemophilia A	None	None
Australia	Yes	September, 2020	Moderate and severe hemophilia A	None	Patients must report through the Australian Bleeding Disorder Registry (ABDR) and MyABDR

Prevalence of hemophilia A*

- Severe hemophilia A is defined as a FVIII level of less than 1% of normal. The number of people with severe hemophilia A in Canada (including Québec) is 995 (35% of total cases of hemophilia A).
- Moderate hemophilia is defined as a FVIII level of 1-5% of normal. It should be noted there is little clinical difference between a factor level of 0.9% and another of 1.1%. The difference is likely within the margin of error of the assay. Moreover, other factors besides FVIII level affect clinical severity. The number of people with moderate hemophilia A in Canada is 303 (10% of total cases).
- Mild hemophilia is defined as a factor level of 5-40% of normal. The number of people with mild hemophilia A in Canada is 1,567 (55% of total cases).

* *Data from 2018 World Federation of Hemophilia Global Survey, Canadian Bleeding Disorder Registry and iCHIP (BC).*

CHS OBSERVATIONS AND RECOMMENDATIONS

It is the belief of the CHS that those who will most benefit from Hemlibra will be those patients with severe hemophilia, and those rare cases of people with moderate disease who have a severe bleeding phenotype, many of whom have a FVIII level close to 1%. Hemlibra will be of great benefit to babies and children for whom venous access is the most challenging, both physically and psychologically, and the most disruptive to school, work and family life. It will help avoid the multiple surgeries for the installation and removal of venous access ports (and their morbidity). It will also be of great benefit to those who suffer frequent breakthrough bleeding and joint disease despite prophylactic FVIII therapy. It is critical for those who have difficulty adhering to a regimen of frequent IV infusions (e.g. children, teenagers, the elderly). For these people, all indications are that this therapy will be life-changing.

However, even among those with severe disease, we do not expect a wholesale switch from FVIII to Hemlibra in the short term. In countries around the world where Hemlibra has been available without restrictions to all patients with severe hemophilia A without inhibitors for a year or more, uptake has been gradual (20% to 50% per year). Some are hesitant to adopt a new technology and prefer to wait to see the safety/efficacy outcomes over several years. Others prefer to keep the peak-and-trough nature of factor VIII therapy which is conducive to participation in physical activities (infusions and peak factor levels on activity days, troughs on

quiet days). Some people are accustomed to regular IV therapy, master the technique and are content with the protection against bleeding it offers.

Most likely to switch from FVIII to Hemlibra

- Those at greater risk of intracranial hemorrhage (e.g. newborns). Of course, given their small size and that Hemlibra is dosed by weight, these patients will not use a lot of Hemlibra.
- Toddlers and young children for whom venous access is the most challenging and the most disruptive to school, work and family life. Again due to their small size will not use a lot of Hemlibra.
- Those children and adults who suffer frequent breakthrough bleeding and joint disease despite prophylactic therapy.
- Those people who have difficulty adhering to a regimen of frequent IV infusions (e.g. children, teenagers, the elderly).
- Adults in long-term care in facilities where IV infusions are not possible.

Less likely to switch from FVIII to Hemlibra

- Those who prefer to wait to see the safety/efficacy outcomes over several years.
- Those who want to keep the peak-and-trough nature of factor VIII therapy which is conducive to participation in physical activities.
- Those who are accustomed to regular IV therapy, master the technique and are content with the protection against bleeding it offers.
- Late adopters.

Unlikely to switch from FVIII to Hemlibra

- Those with a mild or moderate disease severity.

These considerations are personal. Judgments as to the most appropriate therapy need to be made by the individual patient/caregiver and the treating physician through a collaborative decision-making process.

RECOMMENDATION

The CHS recommends that Hemlibra be made available to all patients with severe hemophilia, and those rare cases of people with mild and moderate disease who have severe bleeding phenotype. Access to this therapy for those with less severe disease should await more research.

Prescribing conditions

The CHS is in agreement with the CADTH recommendation on prescribing conditions, that is, that patients must be under the care of a hematologist with experience in the diagnosis and management of hemophilia A, more specifically, a clinician in one of the 26 Canadian bleeding disorder treatment centres.

Pricing conditions

The CHS is convinced that Hemlibra represents an important treatment advance for people with hemophilia A. Given the current health crisis, it understands the need to introduce Hemlibra without a significant price premium over the current overall cost of care for hemophilia A;

however, the CHS completely disagrees with the CADTH recommendation that the cost not exceed "the least expensive FVIII replacement." Such a condition ignores:

- The median cost of the six FVIII clotting factor concentrates currently distributed by CBS, which is considerably higher than the "least costly;"
- The current cost of Hemlibra for inhibitor patients. Negotiation of a single, blended price for both inhibitor and non-inhibitor patients would permit huge savings from the inhibitor population which could be used to provide Hemlibra to all in a cost-effective manner;
- The patient input concerning the medical and quality-of-life benefits of Hemlibra compared to FVIII prophylaxis.

Please see the accompanying report in Annex 1 entitled **Canadian Hemophilia Society response to CADTH pricing conditions for Hemlibra**.

SUMMARY OF KEY POINTS

1. FVIII prophylaxis, even starting before the onset of joint bleeding, with optimal regimens, and in adherent patients does not fully protect against long-term joint damage in severe hemophilia A. Outcomes are even less favourable when adherence is not 100%, which constitutes the majority of people. Hemlibra, with greater adherence, has the potential to decrease joint disease.
2. There is good evidence from clinical trials and the real world in over 7,000 patients that Hemlibra offers greater protection against bleeding by maintaining a higher steady-state hemostatic level.
3. The subcutaneous route of administration, compared to intravenous, results in greater adherence to prescribed prophylactic regimens. Easier, less frequent subcutaneous administration of Hemlibra and better bleed protection result in improved quality of life.
4. The introduction of Hemlibra will result in reduction in non-treatment direct costs to the health care system (hospitalization, professional fees, medical tests, medications, disability supports and alternative treatments) and in indirect costs to patients/caregivers (lost wages, productivity and transport).
5. The CHS maintains that by negotiating a single, blended price for both inhibitor and non-inhibitor patients, CBS can provide access for all severe hemophilia A patients in a cost-effective manner.

ANNEX 1

Canadian Hemophilia Society response to CADTH pricing conditions for Hemlibra

Submitted to Canadian Blood Services
January 21, 2021

The Canadian Hemophilia Society (CHS) welcomes the CADTH recommendation that Hemlibra be reimbursed for the treatment of patients with hemophilia A without FVIII inhibitors, but wishes to comment on the pricing conditions contained in the report, and present a different model for establishing a framework to procure Hemlibra in a cost-effective manner for the public payer so that all patients with severe hemophilia A, including those with and without inhibitors, have access to the therapy.

N.B. The Canadian Hemophilia Society does not have access to pricing information. The calculations contained in this analysis are based on certain assumptions and can possibly be refined. Where available, definitive data have been sourced on treatment costs from CBS, on patient numbers from the Canadian Bleeding Disorder Registry and on prophylaxis protocols from product monographs, published research and real-world evidence.

Pricing conditions *— The public payer cost of Hemlibra should not exceed the public payer cost of treatment with the least costly FVIII replacement that is being reimbursed for the prophylactic treatment of patients with hemophilia A without FVIII inhibitors.*

– CADTH report

While the CHS is convinced that Hemlibra represents an important treatment advance for people with hemophilia A, given the current health crisis, it accepts the need to introduce Hemlibra in a cost-effective manner with regard to the current overall cost of care for severe hemophilia A; however, we completely disagree with the recommendation that the cost not exceed "the least expensive FVIII replacement." Such a condition ignores many aspects of hemophilia treatment, namely:

- There are currently six recombinant and two plasma-derived FVIII concentrates distributed by Canadian Blood Services for the treatment of hemophilia A. Their real-world cost varies by a factor of 3 or 4. Some are standard half-life products; others are extended half-life, which have a greater value from a pharmacokinetic perspective. It is illogical to require that, on an annual per patient basis, Hemlibra match the lowest cost among them, unless the goal is only to further push down the cost of hemophilia care rather than to improve health outcomes.
- The CADTH report completely ignores the current cost of Hemlibra for the population of patients with inhibitors to FVIII. When Hemlibra was introduced for the non-inhibitor population in countries such as the U.K., U.S., Australia and France, among others, a single, blended price was negotiated for the entire hemophilia A population, including both inhibitor and non-inhibitor patients. In Canada, the cost of Hemlibra is currently extremely high (though a substantial cost saving in comparison to the combination of FVIII and bypassing agents previously used to treat inhibitor patients). Maintenance of a two-price structure is unfathomable. The introduction of Hemlibra in Canada with a blended price will result in significant savings (in the order of $20,000,000 per year, 65 patients with savings of at least $300,000 per patient per year) in the cost of care for the approximately 65

inhibitor patients currently treated with Hemlibra. Any cost analysis of the budget impact of introducing Hemlibra that ignores this element in the equation is incomplete and flawed.

- The CADTH report appears to focus entirely on a comparison of the drug costs between FVIII and Hemlibra prophylaxis and ignores the reductions in other health care costs that will result from a therapy that reduces the burden of both disease and treatment.
- While the report summarizes patient input regarding current burden of disease and treatment, and the potential for better adherence to treatment and increased quality of life that would result from a subcutaneous vs. an intravenous treatment, this qualitative evidence is given no weight in the final recommendations. One wonders about the value of providing the patient perspective to CADTH when it appears to be ignored.

The cost-effectiveness analysis conducted by CADTH is based on the price for Hemlibra as submitted by the sponsor, and the prices of comparators, apparently based on PMPRB data. These prices have little or no resemblance to current or eventual prices for any of these products, which are either the result of competitive tenders or negotiation. Any discussion of QALYs seems futile in a context in which there is little long-term data on how quality of life will change with the introduction of Hemlibra, though real-world testimonials from thousands of patients around the world describe Hemlibra as "life-changing." Moreover, it is well-recognized that the use of QALYs in the evaluation of therapies for rare disorders is problematic. The Canadian Hemophilia Society, therefore, will not attempt to dispute CADTH's cost-effectiveness analysis. We prefer instead to propose a different model for analyzing the budget impact of introducing Hemlibra as per the CHS recommendation and hopefully contribute to a more wholistic understanding of the hemophilia environment.

rFVIII

The CHS is not privy to the price of the "least costly FVIII replacement that is being reimbursed for the prophylactic treatment of patients with hemophilia A without FVIII inhibitors" cited by CADTH. However, publicly available data provided to the CHS from CBS show distribution of 236,707,887 IUs of rFVIII in 2019-2020 at a total cost of $105,548,016 for an average per IU cost of $0.45.

For this model, the CHS is making certain assumptions:

- An average FVIII dose of 35 IUs/kg 3 times a week, based on product monographs that vary from 20 to 50 IUs/kg, 2 to 4 times weekly.

  N.B. Canadian Bleeding Disorders Registry (CBDR) reports that the average number of doses per week in severe patients is 3.05 and that the average dose among severe patients in all weight classes to be 2,073 IUs (personal communication, January 14, 2021, with Dr. Arun Keepanaseril, project manager, CBDR).
- The number of missed prophylactic doses (due to poor adherence) is offset by the additional FVIII needed for breakthrough bleeds and surgery.
- 100% of children 0-14 with severe hemophilia are on prophylaxis.
- 70% of children 15 years and older and adults are on prophylaxis.
- 90% of FVIII distributed by CBS is used for prophylaxis; 10% is used for on-demand therapy in mild and moderate hemophilia.

This results in utilization rates and costs of:

- 436,800 IUs per year for an 80-kg adult (35 IUs X 80 kg 3X per week X 52 weeks) X $0.45 = $196,560
- 218,400 IUs per year for a 40-kg 12-year-old (35 IUs X 40 kg 3X per week X 52 weeks) X $0.45 = $98,280
- 81,900 IUs per year for a 15-kg 3-year-old (35 IUs X 15 kg 3X per week X 52 weeks) X $0.45 = $36,855

Data from the Canadian Bleeding Disorder Registry (reduced by 22% to account for Quebec) for 2019 identifies:

- 581 patients with severe hemophilia A in the adult age categories, therefore 407 on prophylaxis;
- 183 patients with severe hemophilia A in the 5-14 age category;
- 61 patients with severe hemophilia A in the 0-4 age category.

According to this model, the cost of prophylaxis would be:

- $196,560 X 407 = $79,999,920
- $98,280 X 183 = $17,985,240
- $36,855 X 61 = $2,248,155

This results in a total cost for FVIII prophylaxis of **$100,233,315**

This compares closely with the total cost of prophylaxis FVIII as reported by CBS for 2019-2020 of $94,993,214 ($105,548,016 minus 10% for on-demand use).

Hemlibra

The CHS estimates the current price of Hemlibra for inhibitor patients at approximately $100/mg (85% of the price quoted in the sponsor's submission to CADTH of $3,661.52 per 30 mg/mL vial or $122 per mg X 85% = $100/mg).

This gives current per patient costs of …

- $624,000 for an 80-kg adult patient
  (1.5 mg/kg/week = 120 mg/week X 52 weeks = 6,240 mg/year = $624,000)
- $312,000 for a 40-kg patient
  (1.5 mg/kg/week = 60 mg/week X 52 weeks = 3,120 mg/year = $312,000)
- $117,000 for a 15-kg child
  (1.5 mg/kg/week = 22.5 mg/week X 52 weeks = 1,170 mg/year = $117,000)

Assuming the same age distribution among inhibitor patients as among non-inhibitor patients, and assuming a total of 65 inhibitor patients on Hemlibra, there are 46 patients in the 80-kg category, 14 in the 40-kg category and 5 in the 15-kg category.

Current costs would be …

- $28,704,000 for the 80-kg category (46 X $624,000)
- $4,368,000 for the 40-kg category (14 X $312,000)
- $585,000 for the 15-kg category (5 X $117,000)

Total: $33,657,000

rFVIII and Hemlibra

Therefore, the total cost of FVIII prophylaxis for both inhibitor and non-inhibitor populations is currently approximately $94,993,214 + $33,657,000 = **$128,650,214**.

Future costs for Hemlibra

If all severe patients were treated with Hemlibra at a price of $36.50/mg, total costs would be **$128,428,170**, which is equivalent to current costs for prophylaxis for inhibitor and non-inhibitor patients:

Weight	# of inhibitor patients	Dose/Price	Cost	Weight	# of non-inhibitor patients	Dose/Price	Cost
80-kg	46	6,240 mg X $36.50 = $227,760	$227,760 X 46 = $10,476,960		407	6,240 mg X $36.50 = $227,760	$227,760 X 407 = $92,698,320
40-kg	14	3,120 mg X $36.50 = $113,880	$113,880 X 14 = $1,594,320		183	3,120 mg X $36.50 = $113,880	$113,880 X 183 = $20,840,040
15-kg	5	1,170 mg X $36.50 = $42,705	$42,705 X 5 = $213,525		61	1,170 mg X $36.50 = $42,705	$42,705 X 61 = $2,605,005
			$12,284,805				$116,143,365
TOTAL = $128,428,170							

Conclusions

The cost effectiveness analysis needs to take into account the considerable savings that can be generated by negotiating a single, blended price for all severe hemophilia A patients, including those with inhibitors, as other jurisdictions have done successfully, as well as the non-drug reductions in health care costs.

The CADTH recommendation to reduce the sponsor's proposed price by 89% to compete with the lowest priced FVIII does not consider the entire hemophilia A context. Such a price reduction, as per the CADTH condition, is not necessary to even achieve cost neutrality. A single, blended price of $36.50/mg, a 70% price reduction compared to the price quoted in the CADTH submission, would be cost-neutral in drug costs alone, in comparison to the current cost of prophylaxis with FVIII and Hemlibra for non-inhibitor and inhibitor patients.

The Canadian Hemophilia Society maintains that it is possible and necessary to find agreement such that all patients with severe hemophilia A have access to Hemlibra, if they and their clinicians so choose, in the very near future.