

CADTH COMMON DRUG REVIEW

Patient Input

emicizumab (Hemlibra)

(Hoffmann-La Roche Ltd.)

Indication: Bleeding prevention, hemophilia A

CADTH received patient input from:
Canadian Hemophilia Society (CHS)

July 22, 2020

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

**Submission to the
Canadian Agency for Drugs and Technologies in Health (CADTH)
by the Canadian Hemophilia Society on Hemlibra®**

Name of the drug and indication	Hemlibra® (emicizumab)
Name of the patient group	Canadian Hemophilia Society (CHS)
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July 13, 2020

1. About our patient group

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 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 125 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 ...

- 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 and;
- maintaining the independence of our organization in representing the needs of people with bleeding disorders.

Charitable Registration: 11883 3094 RR 0001

Website: www.hemophilia.ca

2. Information gathering

The CHS has gathered information on the patient perspective in a number of ways.

Hemlibra® has been in use around the world (in clinical trials, for compassionate access and as an approved therapy) since 2016 for patients both with and without inhibitors to factor VIII (FVIII). As of June 2020, over 6,500 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 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. 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 in SECTION 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 recent World Summit of the WFH, held virtually from June 15-19, 2020. Sessions presented the latest research on coagulation therapies, including Hemlibra.

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 SECTIONS 3, 4, 5 and 6.

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. Disease experience

Summary of responses

Patients and caregivers described many impacts of hemophilia. Because of the risk of bleeding and the consequences of past bleeding on joint health, hemophilia continues to limit many people's ability to participate in normal activities of daily living. Worry about breakthrough bleeding (bleeding in the presence of prophylactic treatment) causes stress, anxiety and depression in both patients and caregivers. Bleeding continues to occur despite the current prophylactic treatments. Given the high frequency of infusions of FVIII, accessing veins is difficult and time-consuming for many. Many people mention difficulty in adhering to prophylactic regimens. This is an important factor in sub-optimal outcomes and a key concern for patients, caregivers and health care providers. Pain is only mentioned by a minority of respondents; this is likely under-reported as pain is a long-term everyday reality. Finally, a number of socio-economic impacts related to the burden of disease and treatment are mentioned by respondents.

Impacts of hemophilia, key difficulties (number of similar answers in parentheses out of 52 people surveyed)

- Limits to normal activities of daily living (15)
- Worry about breakthrough bleeds (12)
- Stress, anxiety, depression (11)
- Frequent bleeds despite prophylaxis (10)
- Difficulty accessing veins (10)
- Time needed for infusions (9)
- Damage to joints (8)
- Pain (6)
- Difficulty adhering to treatment schedule (5)
- High frequency of treatments (4)
- Reduced mobility (3)
- Time to travel to hospital (3)
- Difficulty to exercise (3)
- Loss of independence for parents (3)
- Difficulty in planning life because of burden of care (3)
- Time missed from work (2)
- Limited ability to contribute to society (2)
- Difficulty finding, keeping work (2)
- Vein health (2)
- Difficulty in travelling with factor supplies (2)
- Financial impact of frequent hospital visits (2)
- Time missed from school
- Concern about inhibitor development
- Short half-life of treatment
- My child's self-esteem
- Having to stop working in order to care for child
- Stocking inventory of factor
- Caregiver burden
- The unpredictability of bleeds
- The worry over risk of infection during infusions

- The burden of infusing via a port-a-cath in the morning before work and school
- Impact on siblings

The full list of verbatim responses is available on request. These are typical comments.

“Multiple treatments every week, massive doses to achieve coverage, constant inhibitor concern, seeing peers enjoying events not requiring treatments, vein access troublesome, short half-life of current meds, assured of bleed without meds.”

“As the caregiver of a severe hemophiliac, the impacts of the disease on our daily life are huge. We struggle to plan because of the inability to know when hospital care (which is far away for us as we are rural) will be required for a bleed. Because of this and especially when he was younger, we made the choice that one of us would not work to stay home to care for him. We are seeing emotional impacts on our son as he is growing up and insecure about which activities he can do or having to pull out of activities because of bleeds. One of the biggest impacts though is the constant needles. Our son has to treat every other day due to a short half-life and that takes an emotional and physical toll on all of us and then if he has a breakthrough bleed, the frustration and exhaustion is compounded by even more needles.”

“Having to do prophylaxis treatments every 2 days is quite mentally taxing not only on myself, but on the person who helps me. The only veins I can constantly hit are in my left hand, which means I need someone else there to screw on and inject the medicine while I’m holding the needle steady. Overall treatments take about 30 minutes, every two days. This averages out to 15 minutes a day or roughly 1% of my day, or 1.5% of my waking hours. Therefore, doing treatments uses up 1-1.5% of my life. If I live to be 80 years old, 0.8-1.2 YEARS of my life, and my caregiver’s life, is completely dedicated to giving me treatments.”

“I have to give my son a needle every second day. This is time consuming and sometimes very difficult to get/keep a vein. Sometime 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. He's missed basketball, had to opt out of a curling tournament, missed birthday parties, he's had to give up his karate class, his cross-country skiing course. This is the most difficult aspect of the illness.”

“Infusions via a port every 24-48 hours take roughly 30 minutes to perform, making our mornings very hectic. Taking time away from work to nurse injuries, attend physio, etc., has made it difficult for one caregiver to maintain full-time employment. The child with hemophilia gets frustrated with missing out on activities when nursing injuries. Many family members experience anxiety due to the diagnosis and treatment.”

4. Experiences with currently available treatments

Summary of responses

Most patients with severe hemophilia A and almost all those answering this survey report that they are on a prophylactic regimen. IV infusions are administered by the patient himself or his caregiver between two and seven times per week. The main difficulties described are, understandably, venous access and, for many, the long distances to their treatment centre for check-ups, treatments or to pick up factor supplies for home use. Time lost from school and work is a consequence of the challenging treatment regimen.

Reported frequency of infusions via IV or port-a-cath, a surgically implanted device under the skin in the chest to allow for frequent IV infusions (N.B. Frequency of infusions was not specifically asked in the survey.)

Every day	10	(365 times per year)
4 times per week	1	(208 times per year)
Every second day	13	(183 times per year)
3 times per week	6	(156 times per year)
Every 3 days	1	(122 times per year)
2 times per week	8	(104 times per year)
Once a week	1	(52 times per year)
On demand	2	(variable depending on patient's bleeding pattern)
No answer	10	
Number surveyed	52	

Benefits, side effects, burden of treatment (number of similar answers in parentheses)

- Difficulty accessing veins (24)
- Long distance to clinic for treatment or to pick up factor supplies (11)
- Time lost from work for patient/caregiver (7)
- Damaged veins (5)
- Short half-life of factor (5)
- Breakthrough joint bleeding (5)
- Need for a port-a-cath or picc line (5)
- Time lost from school (3)
- Multiple weekly treatments (2)
- Frequent hospital visits (2)
- Stress and anxiety related to infusions (2)
- Damaged joints
- One person in the couple needing to stay home
- Caregiver had to stop working to care for son
- Concern over inhibitor development
- Need for corrective joint surgeries
- Strain on caregiver
- Co-morbidities (autism)

The full list of verbatim responses is available on request. These are typical comments.

“Short coverage, multiple weekly treatments, massive doses required, vein access difficult, missed work from bleeds, joint damage, need for multiple veins.”

“My son has a very low half-life and so he requires a lot of factor and since not having a comparable long half-life factor to Eloctate available to us we have had to go back to Kovaltry. Even on Eloctate he was still treating every other day. My son is now treating himself before he goes to school. Sometimes he is late for school if it was a struggle to get into a vein and had to try several times. When he was younger, he was often late for school after trying to get into a vein up to three times. It is great that we have treatment available to us that allows him some involvement in physical activity. Our son is currently managing himself at home but when he was younger, we had an hour and a half drive to get to our care team for treatment. We would spend 3 hours driving at minimum once a week but most weeks we were driving in 2-3 times a week for treatment. This schedule was the main contributor to our decision to have one parent home to care for him. The cost of travel was significant. Over the years his vein access has been up and down, sometimes good and sometimes bad. He has tracking along his veins in his hands from where he treats so the bruising on his hands is visible. Several times he has had to do daily treatments up to six weeks at a time, using the veins so often they become difficult to access and requires more than one poke on a day which then significantly increases the damage to his veins and the difficulty in using them again. Even with every other day treatment he has damage to his veins that makes treatment difficult.”

“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 the 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.”

“Currently my parents help me with my needles and they are shiftworkers so they need to book off work to help sometimes. I tried going to my on-campus nurse but the first few sessions took over an hour each, they couldn't hit the vein, and they didn't seem to know what they were doing.”

“I had to quit working to stay at home because daycare wouldn't take him. I ended up having to move for cheaper living on one income. Trying to get access to his port is sometimes difficult and need more than one poke at times.”

“My 6-year-old son receives infusions of 1,000 IUs 3 to 4 times per week. I have to coordinate each sports activity or gym course accordingly by calculating the approximate level of FVIII in his blood, which is very laborious. Sometimes, we are unable to infuse and have to go to the hospital. He misses school and my husband and I accompany him to hospital. This means missing a full day of work and parking fees. It has happened that we had to go back again the next day because of venous access issues. Over 6 years we have worked very hard to get our son to accept that we infuse him at home but unfortunately, due to the high number of infusions each week, he still occasionally refuses. We have to keep him home and try again the next day.”

5. Satisfaction with current treatment

Treatment satisfaction

Very satisfied	5
Quite satisfied	13
Somewhat satisfied	15
Not very satisfied	5
Not at all satisfied	3
No answer	11
Number surveyed	52

Summary of responses

Most patients and caregivers report that current factor therapies are quite effective in stopping/preventing bleeds. However, the short mean half-life of approximately 12 hours means that FVIII levels return to baseline (less than 1% of normal) in 2 to 3 days and breakthrough bleeds occur, despite prophylaxis. A higher frequency of infusions can combat this, but at the cost of increasing challenges in venous access as well as increased cost.

Comments on current treatment (number of similar answers in parentheses)

- Good efficacy to stop/prevent bleeding (13)
- Doesn't last long enough (short half-life), high frequency of treatment (12)
- Breakthrough bleeds despite prophylaxis, insufficient protection (factor level) (6)
- Difficult/time consuming to administer (3)
- Ongoing development of target joint

The full list of verbatim responses is available on request. These are typical comments.

"Somewhat. I am so glad that there is some type of treatment available so that our son can have some normality in his life as far as involvement in activities at schools and with friends and when he bleeds there is something we can do to stop it but I am frustrated with so many needles. Not that satisfied. Frustrated with the breakthrough bleeds. Very frustrated."

"Mostly satisfied. It's definitely a lot better than what I'd expected when he was diagnosed, but he is still experiencing breakthrough bleeding even with treatments every other day."

"Moderately satisfied. 10 bleeds in last year despite prophylaxis."

"Very satisfied. Our son responds well to treatment."

"Somewhat satisfied. Despite everything, he still has unexplained hemorrhages."

6. Improved outcomes

Summary of responses

The clear desire among the vast majority of respondents is to have less frequent treatments, preferably not needing IV access and, at the same time, achieve better protection from bleeding. Such advances would, they believe, reduce worry and stress, allow them to be more active and less dependent on health services, and result in less absenteeism from school and work for both patients and caregivers.

Desired improvements (number of similar answers in parentheses out of 52 people surveyed)

- Longer lasting treatment (half-life), less frequent administration (30)
- Better protection from bleeding (higher trough level) (15)
- No need for venous access (10)
- Easier mode of delivery (10)
- Once-a-week treatment (5)
- Subcutaneous treatment (5)
- A pill (3)
- Constant factor level (3)
- Once-a-month treatment (2)

Differences in quality of life

- Less worry, stress (7)
- Capacity to be more active (5)
- Less dependence on health services (5)
- Less damage to veins (3)
- Fewer visits to clinic (3)
- Less time needed to treat (3)
- Less time lost from work (2)
- Capacity to contribute more to society (2)
- Able to travel, take family trips (2)
- Still have a concern over new therapies, hesitant to switch (2)
- Less burden on caregivers
- Access to treatment closer to home
- Easier to maintain adherence
- Less impact on siblings
- Improved family quality of life
- Less pain

The full list of verbatim responses is available on request. These are typical comments.

“Better and longer lasting results. Easier treatment options, I'd love to be able to administer meds without veins!! That would be HUGE!! I'd sure be more of a contributor than a dependant. I'd be less of a dependant on health services. I'd be able to enjoy life and activities I've only been able to observe my peers do. I would be able to live a life I only dreamed of. I don't know how words could fully express the improvement this new med would provide. I'd be living a dream!!!”

“I would really like to be able to take factor once a week or less rather than every day. It would make a huge difference in my day-to-day.”

“Less needles! Longer and better rise in his factor levels leading to better coverage. Our lifestyle would be drastically changed if our son’s factor level would be more constant! The constant worry of him getting a bleed because his level is low and therefore susceptible would be a game changer in our decision making. We would have the freedom to allow him to participate in activities away from home like school trips. Not being on call 24 hours a day would mean that I could decide to go back to work or even commit to activities with greater certainty that they would happen. We could more freely make decisions to go on family trips and be further away from our care team. Most of all our first thought every time we want to do something fun wouldn't be what we have to do to be able to give our son a needle and get him to care if he gets a breakthrough bleed because his factor levels were bottomed out.”

“Treating once a week under the skin is our ultimate wish.”

“A simpler treatment would be amazing. Accessing a port-a-cath (especially with an autistic child) is a two-person job at the best of times, and there is a lot of training that goes into being able to perform this skill. This leaves the responsibility solely on mom and dad. Mom would be able to work a better schedule if this was a treatment that was easier to administer.”

“A product that lasted longer and which significantly increases the FVIII level would improve our quality of life. There would be less stress related to the repeated infusions and therefore more collaboration from my child, and less stress that my child will bleed as his factor level would high enough, less stress to do the infusion, less jealousy from my other child who feels he receives less attention, fewer medical appointments, and better overall family atmosphere. Globally, I'd say the majority of decisions about family activities and permissions granted to the children are dictated by hemophilia.”

7. Experience with drug under review

To date in Canada, access to Hemlibra has been restricted to people with hemophilia A and inhibitors, and a small group of approximately 15 people with hemophilia A without inhibitors who were granted compassionate access starting in autumn 2019. The improvement in health outcomes and quality of life has been dramatic.

The Association of Hemophilia Clinic Directors of Canada (AHCDC) conducted a survey in June 2020. Questionnaires were sent to health care providers in 12 bleeding disorder treatment centres caring for 14 patients. Thirteen (13) surveys were returned.

Treatment outcomes

The median age of patients at the time of application to the program was 11 years, with a range of 13 months to 65 years.

Treatment prior to switching to Hemlibra:

- Eight (8) patients on standard half-life FVIII, average of 3.7 infusions per week
- Three (3) patients on extended half-life FVIII, average of 2.6 infusions per week
- Two (2) patients on extended half-life FVIII, on-demand infusions

Eleven (11) target joints were reported in eight (8) patients before starting Hemlibra.

The mean annual bleeding rate (ABR) before starting Hemlibra was 5.46, median 3. (Omitting the two (2) on-demand patients, the mean ABR was 3.5.)

The cumulative time on Hemlibra at the time of the survey response was 1,731 patient days (mean 133 days, median 147 days).

Nine (9) of the 13 patients had zero bleeds on Hemlibra.

Three (3) definite bleeds were reported on Hemlibra, two (2) of which were traumatic; two (2) FVIII treatments were administered for events judged as questionable, but were likely not bleeds.

Health care provider observations and comments on patient/family quality of life

“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 flush 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.”

Testimonials submitted to the CHS

“Along with severe hemophilia A, my son suffers from autism spectrum disorder and severe global developmental delay. From the time [REDACTED] 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 completely 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. [REDACTED] 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."

- Submitted by the mother of a 4-year-old from Saskatchewan, June 27, 2020

Free at last

"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.*

I've never been able to take part in physical activity without asking myself whether I should have clotting factor concentrates on hand.

In my youth, a hemorrhage meant three weeks of hospitalization with continuous blood transfusions as treatment! According to my report card, I missed three months of school in Grade 3.

At a very young age, my parents taught me to take responsibility and take care of myself. I remember very well one morning when I was five or six and I was in a rowboat at a hunting camp with my father. He gave me a pocket knife and said "André, I know you'll want to take my knives one day. I'm giving you this knife so you can use it safely." Then he showed me how to lock the blade, to always push it, never pull the blade towards you, and to close it.

With hemophilia, HIV, hepatitis C and inhibitors, the whole ARMY OF DAMOCLES was hanging over my head. If only I had had a treatment like Hemlibra to give me some semblance of a normal life.

My parents were smart enough to let me judge (in part) what activities I wanted to do. That way, I was able to play tennis and badminton (up to university) and take part in other non-contact activities, such as canoeing, hunting and fishing, safely and without having clotting factor concentrates with me.

I'm now 62 years old, and despite all the obstacles in my life, I still managed to become a grandfather. Unfortunately, my grandson inherited my severe Type A hemophilia. He deserves to have a normal life and not, like me, end up in a coma for an entire summer. I fell on a piece of wood and perforated my digestive tract, which caused uncontrollable generalized abdominal bleeding and meant I needed blood transfusions.

*My grandson received Humate-P at the Centre Mère-Enfant de Québec hospital, and the nurses had to **try three times to place the catheter needed** for a large volume of infusion! For a 10-month-old baby, it could **be traumatizing to be tortured like that** and could end up making him afraid of hospitals. This would be understandable but unfortunate given his severe hemophilia!*

Shouldn't we offer parents of children with hemophilia the best treatment available? Isn't caring for a disabled child a heavy task in itself?

Having a child with severe hemophilia is already an onerous responsibility, so why complicate it with painful and aggressive intravenous fluids and catheters?

I hope that as a society we will provide the best for children with hemophilia and their parents."

- Submitted by a person with severe hemophilia A
Québec City, June 19, 2020.

"My spouse has severe factor VIII hemophilia and has been using Hemlibra for five months.

As his partner for more than 35 years, I've witnessed many hemorrhages—small, major, serious, severe—with all the destructive consequences for his joints. We've raised our children through periods when Daddy was on crutches, in pain and even about 10 years in a wheelchair. I will not talk to you about the AIDS and hepatitis C disaster and the impact on the whole family since this is not the purpose of my writing.

Thanks to Hemlibra, he hasn't had a single hemorrhage for the past five months, not even a bruise! We've never experienced this before. One less sword of Damocles over his head, over mine and over those of our daughters, who have always known their father to be suffering and/or ill. Unfortunately, in his case, this treatment has come too late for his severely damaged joints. He lives with pain day and night. I live with someone who suffers all the time. Can you imagine the consequences for the life of a couple and a family?

I'm sharing this with you because we recently had a grandson with severe hemophilia just like his grandfather. He will start walking soon with the prospect of more frequent visits to the hospital, especially when he starts prophylaxis. His parents have had to take him in for an injection to stop the hemorrhage only twice so far. It took five hours each time, which is much better than the weeks of hospitalization my spouse experienced as a child. Medicine has come a long way, but it's still a five-hour wait with a baby, during which doctors in the emergency room ask many questions, concerned about the slightly suspicious "bruises." Parents are not always listened to when they explain the importance of intervening quickly to stop the bleeding.

As a young couple, we wanted to have children. But I felt guilty in thinking that if we had daughters, they would face the tough decision of whether to risk having a boy with severe

*hemophilia. At the time, my spouse reassured me that there would be new treatments for hemophilia in 30 years. Well, here we are. I think of our grandson who, thanks to Hemlibra, will not have bruises scattered all over his body—the pain, the crutches, the deformed joints, the hours spent in hospital, the school absences or the restrictions of all kinds. It's my dearest wish that our daughter and her partner **never have to go through** this with their son.*

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.

The blood system failed to live up to its responsibilities in the 1980s with HIV and hepatitis C. You could make a difference in 2020 by allowing those with hemophilia to lead more normal lives.

This would be a remarkable achievement for the entire health care system.

Thank you for your attention to my request.”

- Submitted by the spouse of a man with severe hemophilia, mother of a daughter who is going through a great deal of worry, and grandmother of an adorable little boy.

Quebec City, June 19, 2020.

8. Companion diagnostic test

No comment.

9. Research highlights

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.

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. 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. BMC Hematology (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 on-line 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
Germany	Yes	February 2019	Severe hemophilia A	None	None

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 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 creation 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% or less per year). Many 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). Many others 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.

Key messages

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 6,500 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.
4. Easier, less frequent administration of Hemlibra and better bleed protection result in increased quality of life.
5. Uptake of Hemlibra will be gradual. In addition to those people choosing not to switch, FVIII will continue to be needed in some other situations: immune tolerance induction of previously untreated patients (possibly low dose FVIII combined with Hemlibra, rare cases of breakthrough bleeding and in some surgical procedures.

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.

APPENDIX: Patient group conflict of interest declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Yes. Physicians from the Association of Hemophilia Clinic Directors of Canada (www.ahcdc.ca) and other health care professionals provided treatment outcome data and patient-reported outcome comments from 14 of the 15 patients with hemophilia A without inhibitors receiving Hemlibra via compassionate access. (See Section 7.)

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Yes. Data provided through the PROBE study. See <https://probestudy.org>.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

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 FVIII)				X
CSL Behring (manufacturer of FVIII/VWF)				X
Octapharma (manufacturer of FVIII)				X
Pfizer (manufacturer of FVIII)				X
Roche (manufacturer of Hemlibra)				X
Sanofi (manufacturer of FVIII)				X
Takeda (manufacturer of FVIII)				X

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 patient group in a real, potential, or perceived conflict of interest situation.

Name: David Page
 Position: National Director of Health Policy
 Patient group: Canadian Hemophilia Society
 Date: July 13, 2020