CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: **Berotralstat (Orladeyo)**
Indication: Hereditary Angioedema (HAE)
Name of Patient Group: HAE Canada (HAEC)
Author of Submission: HAEC Advocacy Committee

1. About Your Patient Group

HAE Canada (haecanada.org) is dedicated to creating awareness about HAE and other related angioedema, to help speed the diagnosis of patients, and to enable them to become champions for their own quality of life. We equip patients, caregivers, family members and health care providers with the information, tools and resources they need to ensure that those with HAE and other related angioedema can live healthy and productive lives. Additionally, HAE Canada is committed to improving patient access to Health Canada approved treatments for hereditary angioedema.

2. Information Gathering

In February and March 2022, HAE Canada (HAEC) attempted to contact patients who had experience with Berotralstat (Orladeyo). HAEC emailed our membership and contacted three Canadian physician investigators who had patients enrolled in the APeX-2 Study and asked that they connect these patients with HAEC so that we could get their insights regarding their challenges with hereditary angioedema and experiences with berotralstat for *the routine prevention of recurrent attacks of hereditary angioedema*. Three patients provided comments to HAEC about their experience with berotralstat. (Note: The APeX-2 study had very few Canadian participants with 3 of 47 study sites in Canada, with a total of 121 patients enrolled globally. Identifying and contacting patients with experience with berotralstat is extremely difficult).

Also, in 2021 HAE Canada conducted our 2nd National Report Card survey, offered in English and French, of patients and caregivers to better understand the needs and experiences of patients with HAE and to inform HAE Canada's policy and advocacy activities related to improving access to safe and effective treatments.

Additionally, in 2020, qualitative interviews, using a semi-structured interview guide, were conducted by HAE Canada with eleven (11) patients with a mix of either Type 1 or Type II HAE to better understand and characterize patient patterns of use for treatments for HAE. The interviews included questions and discussion on patients experience with HAE attacks, their experiences with HAE treatment, the needs and challenges of living with HAE and their experiences with services related to treatment use and supply.

And, in 2019 HAE Canada conducted two surveys to gain insight into patient experience and expectation with therapies used to treat hereditary angioedema. The surveys were in support of the HAEC patient submission to CADTH with respect to lanadelumab (Takhzyro) and to the HAE Forum organized by Canadian Blood Services with respect to C1 Esterase Inhibitor Subcutaneous [Human] (Haegarda).

This report reflects the results of our surveys regarding patient experience with HAE treatments, and patient commentary specific to the use of berotralstat, as well as insights HAE Canada has garnered from more than a decade of experience in patient support and advocacy related to hereditary angioedema.

3. Disease Experience

Hereditary angioedema (HAE) is a severely debilitating and life-threatening disease. It manifests as unpredictable, recurrent/intermittent edema attacks in different parts of the body including the gastrointestinal tract, upper respiratory tract, extremities and face. Gastrointestinal (GI) attacks are common in HAE, with severe abdominal pain and other GI symptoms. Untreated laryngeal attacks may result in asphyxiation and death. Swelling in other body parts can also significantly interfere with patients' daily pursuits, resulting in severely impaired quality of life.

Patients may still be affected by HAE even after the physical symptoms of an attack abate. For many, the expectation of HAE attacks imposes harsh limits on activities and plans. Due to the unpredictable nature of the disease, many patients experience high levels of distress and anxiety in everyday life, often attributed to: restricted or disrupted social life, anxiety due to fear of future attacks, the concern of HAE being passed to their children, and disruption/interference in educational and career pursuits. Many patients report that they do not pursue higher education due to HAE, and that they deliberately elect to not seek out certain jobs, and job advancements, due to expected recurrent edema attacks

We asked in our 2019 survey: *On a scale of 1 - 5* ***please rate how Hereditary Angioedema impacts or limits your life and day-to-day activities****. 1 is "not at all" and 5 is "significant impact".* We had 6 categories as follows:

Rate how Hereditary Angioedema impacts your ***Ability to Travel*** *N=66*						
1 (not at all)	2	3	4	5 (significant impact)	N/A	Weighted Average (WA)
10pts (15%)	20pts (30%)	11pts (17%)	6pts (9%)	15pts (23%)	4pts (6%)	**2.94**

Rate how Hereditary Angioedema impacts your ***Ability to Exercise*** *N=66*						
1 (not at all)	2	3	4	5 (significant impact)	N/A	Weighted Average (WA)
18pts (27%)	13pts (20%)	9pts (14%)	11pts (17%)	13pts (20%)	2pts (3%)	**2.81**

Rate how Hereditary Angioedema impacts your ***Ability to Work*** *N=66*						
1 (not at all)	2	3	4	5 (significant impact)	N/A	Weighted Average (WA)
14pts (21%)	16pts (24%)	10pts (15%)	8pts (12%)	12pts (18%)	**6pts (9%)**	**2.80**

Rate how Hereditary Angioedema impacts your ***Financial Situation*** *N=66*						
1 (not at all)	2	3	4	5 (significant impact)	N/A	Weighted Average (WA)
26pts (39%)	16pts (24%)	3pts (4.5%)	9pts (14%)	8pts (12%)	4pts (6%)	**2.31**

Rate how Hereditary Angioedema impacts your ***Ability to spend time with family and friends*** *N=66*						
1 (not at all)	2	3	4	5 (significant impact)	N/A	Weighted Average (WA)
23pts (35%)	18pts (27%)	14pts (21%)	6pts (9%)	4pts (6%)	1pt (1.5%)	**2.23**

Rate how Hereditary Angioedema impacts your **Ability to Conduct Household Chores** *N=66*						
1 (not at all)	2	3	4	5 (significant impact)	N/A	Weighted Average (WA)
24pts (36%)	18pts (27%)	12pts (18%)	5pts (8%)	5pts (8%)	2pts (3%)	**2.20**

Patients had an option to add free-form commentary to the question re: **impacts on day-to-day activities**. These are a selection of their comments:

> *"… From the ages of 20-50 I had attacks weekly and it did affect my life adversely. A preventative medicine would have been fantastic when I was younger*."
>
> *"The veil of anxiety coloured my life every day."*

We asked: ***How has hereditary angioedema affected you psychologically/emotionally?***

Patients said:

> *"I nearly died from a laryngeal HAE attack which has profoundly changed all levels of my life"*
>
> "*when i was undiagnosed I experienced a lot of pain (abdominal attacks) and with no diagnosis -- no one believed me"*
>
> *"depending on the location of the attack I have not wanted to go out in public*"
>
> *"Unrelenting source of stress."*
>
> *"Chronic anxiety over the unpredictability of this disease."*
>
> "*Depression, anxiety, feature of future attacks, embarrassment and shame"*

We asked: ***How has hereditary angioedema impacted you financially?*** *(n=65)*

> *61.54% (n=40) reported HAE caused them to miss time at work or be less productive at work*
>
> *21.54% (n=14) reported HAE required them to spend out-of-pocket for medical care*
>
> *9.23% (n=6) reported that HAE has prevented them from securing a job*
>
> *6.15% (n=4) reported hereditary angioedema has impeded their ability to advance in the workplace*
>
> Some patients expounded:
>
> *"Reluctant to advance further due to fear of additional work stressors having a negative impact on my health"*
>
> *"Retired now but it was very challenging to meet the demands of work before I stopped."*
>
> *"My inability to pay for the medication while being a student has left me on welfare"*
>
> *"Caused me to be absent from my job"*

Conclusion: The impact of Hereditary angioedema (HAE) goes well beyond its immediate debilitating and life-threatening manifestations. The majority of our recently surveyed patients/caregivers report having regular fear of unpredictable attacks. These patients experience generalized anxiety and stress along with many other emotional and cognitive impacts. HAE also interferes with patients' daily activities, with the disease having substantial negative impact on many patients' ability to work, travel, exercise, do household chores, and socialize with family and friends. HAE inhibits many patients' ability to pursue higher education

or job advancements, and negatively affects their personal finances due to sub-optimal employment, interference with employment and costs due to treatment for HAE.

4. Experiences With Currently Available Treatments

Areas of Unmet Need

Recognizing the burden to patients associated with HAE, including the ever-present risk of experiencing a life-threatening laryngeal attack, improved preventative treatments are urgently needed. Patients that may have the greatest unmet need for an intervention such as oral, once-daily berotralstat are:

i) Patients who find current prophylactic treatments to be ineffective

There is no current way to predict who will respond best to any current treatment for HAE, and while some patients respond extremely well to certain treatments, others do not. This heterogeneity in response to treatment drives an urgent need for treatment options for Long-term Prophylaxis (LTP).

ii) Patients who experience damage to their veins, or worry about future damage to their veins

For instance, one patient reported during a one-on-one patient interview in 2020*: "I took Berinert IV as prophylaxis twice per week until my veins got so bad …then I was lucky enough to get on the Haegarda drug trial .. which is effectively Berinert SubQ. This gave my veins a rest."* Another patient interviewed in 2020 reported*: "I moved from IV to SubQ because of issues with my veins. I didn't know SubQ was an option. When I found out I moved to it. I was using the same veins too often, which was causing damage…"*

iii) Patients who find it difficult and uncomfortable to self-administer intravenous or subcutaneous prophylactic treatments for HAE

Many patients have reported that they have difficulty self-administering treatment for HAE. This can be a function of a patient having damaged veins, or having difficulty finding a vein for intravenous infusion, or simply having great discomfort or general difficulty with the self-administration of an IV treatment. With respect to the administration of either subcutaneous or intravenous treatment for HAE, some patients have strong needle-aversion which makes an effective oral medication highly attractive to this subset of patients.

iv) Patients who live far away from hospital care

IV HAE treatments have the effect of requiring patients to expend much time traveling to treatment and undergoing treatment; especially if they have difficulty doing home infusions.

v) Patients concerned about risk of infectious agent transmission and supply interruptions / shortages from plasma-derived HAE treatments.

Even though multiple critical steps are taken to minimize the risk of infection from transfusion of blood products, the risk of infectious agent transmission from plasma-derived products, in some cases, drives patient preference for non-plasma derived treatments.

Of importance, Canadian Blood Services (CBS) recognizes that the use and demand for plasma-derived therapies continue to rise globally, while the percentage of plasma-derived products produced from plasma collected at Canadian donor centers is decreasing. While CBS is working to develop capacity to collect more

plasma domestically to address plasma supply issues, an important strategy to lessen demand of these therapies is to also offer patients *non-plasma* derived therapies when such therapies offer the required efficacy, safety and convenience for patients.

Satisfaction with Current Treatments

In our (2021) National Report Card survey, we asked patients: *Please rate how satisfied/dissatisfied you are with the effectiveness of your current HAE treatment to prevent attacks.* (138 patients responded to this question).

Very dissatisfied		Dissatisfied		Neither satisfied nor dissatisfied		Satisfied		Very satisfied		Not applicable		Total
3.6%	N=5	13.0%	N=18	10.9%	N=15	25.4%	N=35	29%	N=40	18 %	N=25	N=138

When adjusting the results to remove the 25 patients for which this question was “Not Applicable” (changing the denominator to 113 respondents) we find that **over 20% of patients are currently *very dissatisfied* or *dissatisfied* with the effectiveness of their current treatment** used to prevent attacks. Numerous patients provided comments about their satisfaction with the effectiveness of current treatments including:

> *“Effective oral treatment would be best”*
>
> *“A better way of administering medication would help”*
>
> *“new, non-blood sourced medication would be preferable -an oral rather than injected medication would be preferred”*
>
> *“I had been on danazol for 30 years, when without warning, there was no supply left in the country - this was EXTREMELY stressful - no drug, no alternative - and had to try to track down my immunologist who was out of the country to figure out what to do. It leaves us on edge. If only this could be given orally, we would be happy”*
>
> *“Hate having to do prophylaxis treatment every second day, would love a pill!”*
>
> *“I am SO sorry to have to say that I am dissatisfied because I appreciate the improvement that Berinert and Firazyr have made to my quality of life overall. However, because my life revolves around needles, my injection schedule and dealing with pain on a daily basis, I have to be honest and say that I am "dissatisfied".”*
>
> *“The injections twice a week around the belly are causing soreness”*
>
> *“Berinert works excellent while I'm having an attack, but I don't find subcutaneous super effective at preventing the attacks.”*
>
> *“Although my medication is all working I do have to do 3 infusions per week in addition to my other treatments so that's a lot of needles! Travelling with so much medication is so difficult as well.”*
>
> *“Would be a lot easier to **not** have to have my wife give me IV prophylaxis twice a week - hard on my veins”*
>
> *“Would like other treatment options”*

"Would like easier admin. Not IV"

"IV starts every 2 days can be exhausting"

".. I would prefer pills to sub-cutaneous injections; however, I am happy that I have access to the medication."

"*Please encourage research to develop an oral medication (pill) that is effective in preventing attacks, so that we can stop sticking ourselves with needles."*

"Really, I just want my life back. ***A pill would make things so much easier*** *than sticking myself with a needle except when I'm having a throat or neck swell. My anxiety is sometimes out of control and if I overthink this disease i can end up with a swell which I turn gives me a panic attack. It's just super frustrating. Things have definitely got better but I'm still infusing an average of 10 times a month which in my opinion is too much. The cluster swells are exhausting."*

"I have been so fortunate that I have had excellent care and treatment. My daughters have just been diagnosed (no symptoms yet) and the only thing I would love to see for them is a pill rather than needles. I have one daughter with an extreme phobia of needles which will present a real problem if/when she requires treatment. I guess the other thing would be more knowledgeable of HAE among the medical professionals as well."

Conclusion: HAE patients, (and CBS) urgently require prophylactic treatments that are more convenient and easier to administer at home, such as oral once-daily berotralstat.

5. Improved Outcomes

Patients continue to seek treatments that better control attacks while offering greater convenience and ease of use. Treatments that eliminate or substantially reduce attacks compared to existing treatments are of critical importance to patients as each edema attack can be severely debilitating, and in many cases life-threatening.

Greater control of attacks would also ameliorate the ever-present anxiety and fear many patients experience due to unpredictable attacks and reduce the negative impact on a patient's ability to work, pursue education, travel, exercise, do household chores, and socialize with family and friends.

We asked, in our 2019 survey to support patient input to CADTH (re: lanadelumab): ***If you were to consider taking a new therapy for your hereditary angioedema please rate the following on a scale of 1 - 5. 1 is "not important" and 5 is "extremely important".*** We had various categories:

Improved management/reduction in attacks of edema (swelling) *n=57*						
1 (not important)	**2**	**3**	**4**	**5 (extremely important)**	**N/A**	**Weighted Average (WA)**
1pt (1.75%)	0pts (0%)	2pts (3.5%)	7pts (12.3%)	47pts (82.5%)	**0pts (0%)**	**4.74**
No direct cost to user/patient *n=58*						
1 (not important)	**2**	**3**	**4**	**5 (extremely important)**	**N/A**	**Weighted Average (WA)**
2pts (3.5%)	1pt (1.7%)	1pt (1.7%)	2pts (3.5%)	52pts (90%)	**0pt (0%)**	**4.74**
Easier mode of delivery as a subcutaneous option *(vs. IV) n=58*						

1 (not important)	2	3	4	5 (extremely important)	N/A	Weighted Average (WA)
2pts (3.5%)	1pt (1.7%)	3pts (5%)	7pts (12%)	44pts (76%)	**1pts (1.7%)**	**4.58**
A more convenient dosing interval/less frequent dosing *n=58*						
1 (not important)	**2**	**3**	**4**	**5 (extremely important)**	**N/A**	**Weighted Average (WA)**
5pts (8.6%)	2pts (3.5%)	5pts (8.6%)	8pts (13.8%)	38pts (65.5%)	**0pts (0%)**	**4.24**

Patients (76%) overwhelmingly are seeking treatments with **an easier mode of delivery**.

The addition of subcutaneously administered lanadelumab (Takhzyro) to the treatment armamentarium for HAE was extremely important. Many patients who had the opportunity to switch to lanadelumab, or try lanadelumab during clinical trials, experienced substantial or total reduction in attack frequency while also benefiting from an easier to use therapy. However, some patients who tried this treatment saw little or no benefit from this treatment, and still require a treatment that offers a more convenient method of preventing HAE attacks.

Conclusion: Of critical importance to patients are therapies with an easier mode of delivery that are effective in preventing attacks and have fewer side effects.

6. Experience With Drug Under Review

In February and March 2022, HAE Canada (HAEC) attempted to contact patients who had experience with berotralstat (Orladeyo). Three patients provided comments to HAEC about their experience with berotralstat. (Note: The APeX-2 study had very few Canadian participants with 3 of 47 study sites in Canada, with a total of 121 patients enrolled globally. Identifying and contacting patients with experience with berotralstat is extremely difficult).

Patient 1: A female patient with HAE who was enrolled in the Apex-2 study, who was on treatment for between 1 and 2 years.

This patient reported having HAE attacks, before starting berotralstat, approximately once per week focused primarily in her extremities (limbs/hands/feet) and in her gastrointestinal system.

Based on this patient's personal experience with berotralstat, she found this treatment to be extremely effective in prevention of attacks of HAE and she also found the side-effects to be easy to tolerate. She reported only noticing one treatment-related side effect "*abdominal pain*" which she rated as being "*very tolerable*".

We asked her: *On a scale of 1-5 how would you rate your quality of life (QoL) while taking berotralstat? 1 is "low/seriously impacted", and 5 is "high/normal living".* She selected "5" suggesting that this treatment afforded her the opportunity to live a normal life. When we asked her *"How has berotralstat changed, or how is it expected to change, your long-term health and well-being?"* She replied: "*No more crises with this treatment"* She added: *It's so easy to add it in daily routine."*

Patient 2: A female patient with HAE who was enrolled in the in the Apex-2 study who was on treatment for between 1 and 2 years.

This patient reported having 1-2 HAE attacks per month, before starting berotralstat, and having approximately 3-4 attacks per month (focused primarily in her gastrointestinal system) while taking berotralstat. Consequently, she found this treatment to not be effective in the prevention of attacks of HAE.

We asked this patient, *if 1 is "completely intolerable" and 5 is "very tolerable" how would you rate berotralstat's side effects?* This patient rated the tolerability of side effect to be a "*3*" (neither *completely* intolerable or *very* tolerable). We asked to identify specific side effects that she experienced with berotralstat and to rate them on a scale of 1 – 5 with 1 "completely intolerable" and 5 "very tolerable". She listed "*abdominal pain*" as a treatment related side-effect and rated it's tolerability a "*3*". She also listed "*diarrhea*" as a treatment related side-effect, and rated it's tolerability a "*3*".

She added: *Orladeyo (berotralstat) was not really effective on me, however, worked very well for my daughter.*

When we asked her "Can you tell us about your story and why access to berotralstat and future therapies are so important to you? She replied: "*It is important mostly for the next generations (my kids and grand-kids)."*

Patient 3: A male patient with HAE who was enrolled in the Apex-2 study, who was on treatment for between 1 and 2 years.

On the issue of treatment choice, this patient reported that he found it extremely important, in the context of shared decision-making with his physician, to be able to make a choice of treatment based upon each different drug's known side effects. He also reported that the mode of delivery for a drug (eg. IV, subcutaneous, oral) was a key factor when making a choice of treatment (with his physician) for his HAE

Based on this patient's personal experience with berotralstat, he did not find this treatment to be effective in prevention of attacks of HAE as he experienced break through attacks every four to five days. He also found the side-effects to be difficult to tolerate.

The patient reported that he experiences other treatments prior to the berotralstat trial. When comparing berotralstat to his previous experience with the treatments Berinert (C1 Esterase Inhibitor [human]) and Haegarda (c1 esterase inhibitor subcutaneous [human] injection) he reports that berotralstat was much harder to tolerate than both Berinert and Haegarda. The side effects he reported experiencing while on berotralstat that he found difficult to tolerate were abdominal pain and diarrhea. Presently he is on a new clinical trial with no serious side effects to report.

We asked this patient: On a scale of 1-5 how would you rate your quality of life (QoL) while taking Orladeyo? 1 is "low/seriously impacted", and 5 is "high/normal living". This patient selected "3" suggesting that this treatment, while not negatively impacting his QoL, also did not afford him any improvement in QoL.

7. Companion Diagnostic Test

The identification biomarkers and development of accompanying bioassays are urgently needed to accompany clinical trials and enable personalized medicine for HAE. Biomarkers are sought because they can be utilized to diagnose, guide therapies, or make predictions regarding the clinical course of HAE.

HAE Canada encourages ongoing research to identify and validate biomarkers for HAE, and to monitor these biomarkers longitudinally to determine their clinical utility and predictive value.

8. Anything Else?

HAE is a heterogeneous disease with complex pathophysiology. Current knowledge cannot provide convincing explanations for the clinical variability of the disease, and despite detailed research and identification of novel defects, a proportion of patients with HAE are still labeled as HAE-Unidentified (HAE-UI) wherein the genetic defect has not yet been identified. More research work is required to uncover different disease endotypes to identify specified targets for therapeutic intervention with the goal of more effective, individualized management of the disease.

These advances may bring new therapeutic modalities for the management of HAE.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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.