CADTH

CADTH Reimbursement Review

Patient Input

GIVOSIRAN (Givlaari)

(Alnylam Netherlands B.V.)

Indication: Acute hepatic porphyria (AHP) in adults.

CADTH received patient input from:
American Porphyria Foundation
Canadian Association for Porphyria

March 19, 2021

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	Givlaari
Name of the Patient Group	American Porphyria Foundation
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

***www.porphyriafoundation.org The American Porphyria Foundation (APF) is a 38 year old, 12,000 member foundation whose mission is dedicated to improving the health and well being of individuals and families impacted by the porphyrias. Specifically , our programs are modeled to heighten awareness and education about the porphyrias for physicians, patients, families, caretakers, healthcare professionals and the general public in the USA and globally. At present, we are assisting patients and physicians in 76 countries and are helping establish support groups in those respective countries. The APF also supports research by locating patients for research projects and funding specific porphyria research. Another major program of the APF is the *Protect the Future* program to mentor the next generation of experts. The APF has an international component with over 300 members from Canada who receive educational materials, participate in research, and are involved in all projects of the APF. .

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include when the data were gathered; if data were gathered in Canada or elsewhere; demographics of the respondents; and how many patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

***As noted, the APF has over 300 Canadian members who participate in our programs and projects. When the APF posted information on the CADTH project on social media and our Enews soliciting personal experiences from Canadian patients, patients from across Canada responded via telephone and email. We have included their responses within the answers in

this questionnaire and submissions by individual patients. Patients from Canada participated in the Givlaari research and many others have been educated on the treatment though the APF educational programs and through the testimonies they read from the many patients around the world who are on Givlaari now and are overwhelmingly positive. One patient commented on social media, ***I've seen the many posts about how Givlaari has changed lives. I was particularly hopeful when I read that a woman had ZERO attacks after being on Givlaari for over a year. That means zero horrible pain and incessant vomiting, frightening rapid pulse and nightmare symptoms.***

Another very important change is associated with the outrageous pain people suffer, ***I have to have a lot of pain meds. My desire is to free from them but I cannot be free from pain meds without being free of attacks. The pain is too much for a person to endure. A doctor with aip said that it was not compatible with life to have attacks with no pain treatment.***

Others on Givlaari said that they had attacks that were treated, but the attacks were not often, and they were not severe. A man shared, ***My greatest hope was to return to work. That dream is coming true as I'm almost finished school, a feat I could never have done without Givlaari. It gave me my life back.***

Interestingly, as Global Director, I speak with patients on Givlaari and often hear this poignant comment, "I have my life back."

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

*** The APF communicates with Patients worldwide on a daily basis and are extremely aware of the their experiences. Desiree Lyon, founder, former Executive Director and now Global Director, suffers from Acute Intermittent Porphyria and has published her journey widely through books, television and print media, websites and social media. Acute porphyria as a life-threatening group of diseases that primarily occurs in attacks to a chronic condition in patients. Acute porphyrias, AIP, VP, HCP and ADP, affect the Central Nervous System and or the skin causing intractable pain, nausea, rapid pulse, paralysis, confusion to hallucination and other generic symptoms. Porphyrias are known as the "little imitator as it has a host of generic symptoms making it hard to identify, particularly because it cannot be diagnosed without porphyria specific tests. It will not show on normal tests.

Many, if not most patients tell us, ***It took me 15 years to be diagnosed. Even then, I had the demeaning experience of being called a drug seeker and hypochondriac. My attacks were so frequent that as soon as one was over another began, thus validating the hypochondriac status in the minds of doctors and family members. We need a treatment that stops us having these devastating attacks.***

Because attacks are serious and can lead to death, they lead to a negative quality of life, including inability to be employed. One patient said, ***I was a healthy executive at a large health care company. I worked very hard and had a good salary and benefits. Then VP hit me, and I was totally debilitated. I suffered terribly and was repeatedly hospitalized. I finally lost my job as I was unable to go to work. My life was a shambles until I was given Givlaari. Life has turned around for me. I want other people to have my experience.***

Most patients cannot hold employment because of the severity and frequency of attacks. The pain alone is so devastating that patients cannot function and is the thread that runs through the stories of all acute patients. In fact, the pain has been described by physicians as among the worst in human kind, thus causing patient to seek pain management as a necessity. One patient describes her pain, ***I read one women who said the pain is like a thousand flaming swords. She said exactly what I feel except Ill add that the pain is like burning glass swirling around in my abdomen. It is so excruciating that it is indescribable.*** Attacks cause elevations of neurotoxins that create neuropathies that often remain throughout life and require major pain treatment. APF Global Director , Desiree Lyon relates, ***Since I suffer continuous chronic pain on a 10 scale, I understand why controlling attacks is tantamount to patients. I also understand that most patients do not desire to be on a steady diet of pain medications.***

Such a demeaning journey is not uncommon for patients. One women has a heart wrenching experience as a patient and now caretaker for her brother, ***Because of AIP, I had to give up my career as a Registered Nurse. The symptoms, including the anxiety, was so severe and debilitating that I could not longer function well in daily life. Finally, menopause has settled my symptoms a bit. Unfortunately, now I am the caretaker advocate for my brother. He has been on disability for 15 years and is worsening. Two lives are unable to be productive because of porphyria. Had we had Givlaari, there would be two productive people living life to the fullest.*** Another caretaker speaks, ***My wife's porphyria rules our lives. I feel inept to care for her but do my best rather than having her hospitalized her whole life. We are desperate to have Givlaari to stop as many attacks as possible. We don't know how much longer she can live with hematin treatment because of the iron and the veins.***

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

***Despite having Panhematin treatment, patients continue to have attacks as it is a treatment primarily to stop attacks, not prevent attacks. In the USA, some patients are prescribed Panhematin infusions to prevent attacks. We are not aware of that practice in Canada. Unlike Givlaari , which is a simple shot, Panhematin is an infusion administered via a central line or a peripheral vein. Although it is very effective to stop attacks, it can cause platelet aggravation and frequent use can cause hepatic iron buildup and injury. Panhematin is usually infused via a picc line or a port as phlebitis can occur with a regular IV. Unfortunately, many patients must surgically replace their piccs and ports up to six times due to blockage and malfunctions.

After lengthy use, a patient faces blockage of their veins with no access, port replacements, phlebitis and in some cases iron overload, thus they seek Givlaari as a treatment but know that Panhematin must also be available to stop and attack. A Patient notes, ***Panhematin saved my life. It is very helpful to halt my attack, but now my veins are collapsed and my port is not working again.*** Thus, it is apparent that Panhematin serves a critical role in stopping attacks but has complications.

Data shows the new treatment, Givlaari , reduces attacks by 70% over a six month period. . We follow many patients on Givlaari in the USA and see they are clearly having less attacks and even no attacks. Since attacks can cause nerve damage and subsequent excruciating burning pain, patients are anxious to reduce the number of attacks.

Although Givlaari is costly, there is a major assistance program to provide access to Givlaari.. Fortunately, those who are not properly insured can access the treatment via the Alnylam Assist program. Patients have made us aware that the reduction in their attacks is also sizeable and has kept them out of the hospital which is not only very costly but burdensome on the patient and family. ZERO attacks are reported in some patients and others relate that they are having fewer attacks and that they are less symptomatic when an attacks occurs. They must , however, have access to Panhematin if an attack occurs. According to experts, it is extremely important to use Panhematin early in an attack for best results. Thus, the combination of Panhematin to stop the attack and Givlaari to reduce the overall number of attacks is the best solution.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Foremost, patients want a cure. However, their realistic goal is to have a treatment to stop attacks from occurring. Reduction in attacks reduces the symptoms and most importantly the excruciating pain, nerve damage and even paralysis that accompanies an attack. These attacks are so horrific that many patients have said, ***I live in fear of the next attack. The horrific pain drives many patients toward treatments that can reduce attacks and the residual damage. This is a very common statement, Acute porphyria patients tell us repeatedly that they have asked God to let them die rather than suffer one more moment of the pain. This is no exaggeration as our Global Director has said that this was her plea in most of her attacks of AIP.

One caretaker noted, ***Hematin made a difference in the life of my daughter in that it stopped her attacks after they began, but it did not stop her attacks from happening. We need a treatment to stop the attacks from occurring, because attacks are so excruciating and can lead to paralysis and death. Givlaari would provide this relief. Even one attack is too many.***

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the

sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

***In the past, Panhematin has been used to stop attacks when they begin. Within the last few years, a cohort of patients had access to Givlaari via clinical trails. Patients were very excited to have access to Givlaari and have spread their thoughts through social media and conversations with our APF staff. Since Givlarri is a monthly shot opposed to Panhematin infusions, Givlaari is an easier treatment to take. Reported side effects of Givlaari include injection site reactions, allergic reactions and nausea. Side effects reported by Alnylam include liver and kidney problems.

Through patient testimonials and lengthy telephone and email interviews, we have gained great insight on the patient treatment experience, including their Panhematin and Givlaari treatments. Both treatments provided a positive life changing affect. As a rule, when they share about Givlaari or the need for Givlaari, they have said that the attacks are fewer in number and less severe on Givlaari. One patient put it best, ***Panhematin saved my life. But as patients , it is much more than just saving our lives. Life giving cancer treatments go further than immediate relief, they provide treatments to have a quality of life. There is not quality unless attacks are prevented.***

One very ill patient who has been a research patients for every trial over the past ten years said, ***I was frightened for my life, because I was at the point that I no longer had veins for Panhematin infusions. Givlaari was my last chance. I was on the Givlaari trials and had immediate success. Some people say it takes a while to gain effect, but for me, I stopped having attacks after my first shot of Givlaari. Life changed. I could return to work. I could return to life.***

Another woman who had been a business executive shared, ***I had a great career and a great life until attacks of variagate porphyria began and quickly took away my career and my life with one life threatening attack after another. Givlaari gave me back my life.***

The reasons we are told are plentiful, including the veins are no longer capable of having infusions of Panhematin. They have had too many ports which require surgery. They cant use a PICC and they cannot bear any more attacks as nerve damage is too prevalent and painful. , Despite side effects of Givlaari and the fact that some patients continue to suffer attacks, most patients want to continue with Givlaari. Fortunately, when patients on Givlaari do suffer an attack, they are prescribed Panhematin, which stops the attack quickly. There may be an exception, but we are not aware. Most patients are desperate and are eager for Givlaari.

In summary, Givlaari can reduce the number of attacks from fewer attacks to ZERO attacks. Since attacks result in hospitalizations and extreme suffering, the change is life altering for patients and caretakers.
Alnylam pays for the DNA tests for many patients so as to assist with diagnosis. Insurance pays for the majority of testing.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

*** There is no Companion Diagnostic with Givlaari.
However, APF distributes a diagnostic primer to most patients. It is written by expert Dr. Karl Anderson who is the Director of the Porphyria Center in Galveston , Texas. He is also available to counsel with physicians on biochemical testing. In addition, Alnylam provides free DNA for any patients who fit the criteria.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

***Acute porphyrias are often referred to as the “little imitators“ as the symptoms are very generic, such as abdominal pain, nausea, rapid pulse, etc. Therefore, it is not uncommon for diagnosis to take up to 15 years. Even after a doctor thinks of porphyria as a diagnostic possibility , the doctor may order incorrect tests or assess the results improperly, particularly since acute porphyrias cannot be diagnosed without porphyria specific tests. Another moniker for acute porphyria is the “tic tac toe” disease. Patients have experienced so much misdiagnosis and subsequent exploratory and incorrect surgeries that they had what formed a “tic tac toe” game board on their abdomens.

Another issue is that the pain of acute porphyria is so brutal that many patients are thought to be drug seekers when they try to explain their pain in seemingly outlandish terms like, “flaming swords, volcanic churning lava, and burning glass.” They are often not believed making the drug seeking tag a viable one with some doctors and nurses. This undeserved tag is demeaning to the patient and is hard to expunge from their records. Because attacks are not only horrific when suffering them, they also can cause chronic nerve damage. Patients fear both. Therefore, Givlaari is extremely important to patients, because it can reduce the number of attacks and in turn, reduce the present and FUTURE suffering. For many, it has exponentially also reduced the amount of pain medication they must take to quell the attack and chronic pain.
One patient sums up how most others feel, ***I'm currently waiting for Givlaari - I will do anything to help accelerate the process.***

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.

1. Did you receive help from outside your patient group to complete this submission? Yes . The APF located Canadian members for the Alnylam Patient Advisory Board. During the meeting of the Patient Advisory Board, the patients wrote their experiences. At the request of the APF, Alnylam provided some of the patient comments from this board meeting. The majority were from the APF.

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. No

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
Alnylam Pharmaceutical				Yes
Recordati Rare Disease				Yes

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: Desiree Lyon
Position: Global Director
Patient Group: American Porphyria Foundation
Date: February11, 2021

BELOW ARE THE INDIVIDUAL PATIENT SUBMISSIONS.

Name: [redacted]
Province: Quebec

I was diagnosed with Acute Intermittent Porphyria in 2001. I consider myself a very resilient person. I try to focus on the present and my future in a very short-term. I learned through the years that even if I can plan ahead doesn't means is going to happen not because I will give up, but because a Porphyria attack may bend me in pain for days.

My first attack, before knowing what I have, I label it as my biggest trauma. I was very young, living in a new country and didn't know anyone. I was studying hard to learn English and to be accepted at school at the same time I was working full time with a dream of starting my own

business. Suddenly, I started having horrible pain in my stomach and my back. One day my boss asked me, Please leave and take sick leave, You looks miserable." Often, I was going to the restroom to lay down on the floor, in a fetus position because the pain was so severe. I went to see my doctor without an appointment in a wheelchair, I couldn't walk anymore, I was begging God for my death. My doctor hospitalized me and put in a feeding tube. I lost my voice and was fully paralyzed wearing pampers.

One of the best days of my life, is when a few days after a neurologist, arrived with my diagnose. He sat on my bed and he gave me a sincere hug asking me to excuse them for not knowing before that I had AIP. It took me two years of physical rehab and more attacks.

My Porphyria journey is long, one of the hardest part is access to the treatment and been heard and understand by medical staff. With Covid-19 people is in panic because is not cure for it or a full prevention. People feel lost because they can't plan on ahead. This is the everyday for me. **I started receiving Givlaari more than 2yrs ago as part of their phase 3 trial. and it has reduced my attacks drastically.** Before, I was every month receiving either hematin or normosong and hospitalizations and many attacks. I hope, I continue to have access to this medicine.

Answering your questions:-

1) What problems do you have with hematin and what is good about panhematin?
The good about hematin:-
-Hematin was a lifesaver when my wife was sick in the hospital in ICU. Hemtain essentially got her back onto her feet after her first severe attack which made her paralyzed.

Name: [redacted]
Province: Ontario

Currently my wife is having weekly treatments of Panhematin/hematin, and she is in fact feeling better in terms of gaining her strength doing everyday activities. It has also reduced the amount of pain killer by 25% got rid of most of the nerve medications. It has also reduced the number of hospitalizations from 12 a years to 2-3 and has given her some independence, hhus helping me as well. However, there are many problems:
-Hematin requires her to use a port as it is a very thick medication. It constantly blocks her port which requires frequent replacement of her port.
-It has some side effects mainly headaches and low grade fever, she usually gets after treatments which usually resolve after a day or two.
-It takes full 24hrs after first dosage before I notice any improvements in her health.
-I also find that over the years, my wife is getting tolerant to the Hematin i.e. I feel that she needs more dosage to have the same effect.
-In her case, she requires weekly treatments to keep her health manageable which makes working, planning for events a bit more challenging.

Having Givlaari reduce the number of attacks would also help reduce the nerve damage and she continues to have. The hematin helps stop the attacks but she needs to not have attacks . They are dangerous and damage nerves that cause terrible chroic pain.

Name: [redacted]
Province: Ontario

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

1. I've been fortunate, given the disease is rare, that the majority of my specialists have been extremely proactive and thorough. The most difficult process is dealing with hospital Emergency staff/doctors because they don't or won't accept the information provided by the patient. Not enough awareness/knowledge about AIP. The majority of healthcare providers have never seen or treated a patient with AIP.
2. Suggested recommended treatment (IV fluids D10W + 0.45NS solution) is not readily available so the Emergency doctors don't give me the proper solution initially which is crucial for my recovery.
3. Listen to the patient. Just because kidney and liver enzymes are high shouldn't suggest alcohol abuse.
4. Research-more research is required to also raise awareness.
5. Neurologists and hematologists play an important part in the life of the patient diagnosed with AIP and are an ongoing necessity.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

1. What treatment options are available?
2. What are the pro's and con's of treatment?
3. Will my condition worsen, at what rate, and what to expect?

Name: [redacted]
Province: Quebec

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

1. Believe me.
2. Follow my case.
3. Control pain
4. A call, a text, a letter, anything from a doctor, asking me how I was doing, letting me know that even if diagnose was not known they believed me and were working in it.
5. Financial help to my parents.
6. More easy access to medical appointments, chats with doctors

Note: After diagnosed, my doctor gave me his personal phone number. Every time I had an attack I texted him then he ordered the treatment and I had my appointment for hematin infusion next day. This was very good. I moved to Mexico and the treatment was not available. I moved to Belgium, I explained to my doctor how my doctor was treating and she accepted to do the same thing. I was texting when start feeling an attack, she gave already 12 prescriptions, she

was calling to set me up for infusion ASAP and this process helped me to have to go to urgences all the time. Then, I moved to NY and after a complain my doctor made a protocol for me.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

1. Statistics of effectiveness for each treatment
2. Secondary effects
3. Insurance coverage

Name: [redacted]
Province: Ontario

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

I can't name five things that would have made the process of getting diagnosed easier. For me it would mainly just come down to more awareness. More awareness in hospitals, and for doctors in general, to be able to spot the disease. I still get told, to this day, by doctors, "... oh porphyria? I've never heard of that.". I had several days where the hospital assumed, I was on hard drugs because they couldn't figure out my symptoms and I progressively got worse. It took 56 days, and two different hospitals, for them to even begin to diagnose me, which in itself was a complete fluke. I can't speak on much more, as I was on life support or mentally unaware, for much of the early stages. I don't have memories from my first day of my flare (nov 24th) until probably February, a few weeks after my many panhemetin infusions. If it wasn't for my mother being the best advocate I could have asked for, and a doctor joining rounds by chance one day, they honestly may never have figured it out.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

1. Is this safe for continued use, or does it have a limit? How often is the treatment? Will it impact my quality of life?
2. What are the side effects, if any, to this treatment? Are they permanent? Are they worse than what I would have to deal with without it?
3. Is this treatment on the safe drug list? Is it something we know for sure won't cause a possible flare up?

Name: [redacted]
Province: British Columbia

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

This is a hard one because so many things could have been different for me. I think they could have done more searching before giving me surgery, I think they could have had better bedside

manner, I think they could have not assumed I was a drug user but instead someone in serious medical distress, I wish more treatments or treatment options were available, but mostly I think more doctors should be versed in rare diseases, and more willing to test for them.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

Well, I would likely have more than 3, but off the top of my head, I would probably want to know what the benefits were, what the side effects are, and how much it will cost me. I know here in Canada we are covered for the most part, but I am also hyper aware that many treatments for diseases such as Porphyria can costs thousands of dollars, and since I am unable to work and have children to worry about, that is a serious concern.

Name: [redacted]
Province: Ontario

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

My five things are wrapped into one and that is to have had a doctor to treat and support me.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

1. How do we keep this on a bearable level?
2. How can we avoid another attack?
3. When can we get started?

Name: [redacted]
Province: British Columbia

There are no specialists near me, but my GP does what he can. In an attack, the best my doctor can do is to make sure I don't lose my electrolytes. My blood pressure runs amuck without Ativan. The pain is all in my ribs, and my front and back. I have a lot of neuropathy, which is severely painful. I I finally had to stop working 2 years ago. The results are disaster! I need treatment badly. As an aside, I was finally diagnosed in Slovenia as my doctor here did not know what was wrong with me.

Name: [redacted]
Province: Nova Scotia

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

1. Doctors had more in-depth knowledge of symptoms not just severe abdominal pain. AIP displays itself in other ways not all textbook which leads to delayed dx.

2. Doctors willing to learn more and understand individual cases.
3. Accessibility to experienced doctors.
4. Accessibility to proper laboratory testing. wrong tests completed no continuity.
5. I wish I hadn't had unnecessary surgery /treatment and dx would have been quicker.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

1. Expected outcome from treatments
2. Side effects and patient monitoring
3. What treatments available and pros and cons of each

Name: [redacted]
Province: Ontario

I am both a patient and a caregiver. Because of severe AIP, I had to give up my career as a Registered Nurse. Now I am now entering menopause, so my porphyria and subsequent symptoms have settled immensely.

Unfortunately, my brother has extremely severe porphyria for at least 15 years. His large bowel was removed requiring a ileostomy and requires antipsychotics to keep his mind clear to function on a daily basis. He suffers chronic depression, loss of strength, neuropathies, severe abdominal pain, cramping and seizures. He has never had a relationship. Despite all the treatments, his disease is worsening, so he is requiring more and more hematin treatments and more frequent hospital admissions with weekly to daily treatments. I am his caretaker/advocate.

If there was a drug available that could prevent this disease from occurring, it would have prevented the damage from our intractable attacks and may even stop my brothers attacks now. If so, he could have some glimmer of hope for a more normal existence, and so could I.

Name: [redacted]
Province: Manitoba

In 1975, after years of my body suffering physically and mentally, I was diagnosed with an acute porphyria by Dr. [redacted], Head of the Cancer Clinic at the Health Science Centre in Winnipeg, Manitoba, Canada. I was 31 at the time. Dozens and dozens of times over the years before diagnosis I had been admitted to the hospital emergency; dozens and dozens of times I had hospital stays, some of which were weeks in duration; dozens and dozens of times I had doctor's visits.
It is extremely important that the government pay for the cost of Givlaari for porphyria patients because:
**Government should fund/pay for the cost of Givlaari for the patient. Porphyria patients cannot afford the enormous costs of Givlaari and without Givlaari the porphyria patient is going to have unsurmountable stress and end up in hospital, at the emergency ward or at the doctor's office.
**Government, by covering the cost of Givlaari could improve health care quality for all patients with acute porphyria.

**Government, by paying for the cost of Givlaari could reduce health care costs and save millions of dollars in patient reduced hospital admittances, emergency entrances and doctor's visits.
**Government should recognize that the patient has already paid in his/her annual taxes for their health care costs, which includes the drug, Givlaari.

Name: [redacted]
Province: Ontario

Thinking about your journey from your symptoms beginning until you received your diagnosis of AHP, what are five things that would have made that process easier? i.e. What do you wish would have happened or could have been done better?

1. We wish Emergency Room Doctors were more aware about the Porphyria disease. This could have helped doctors to come to right diagnosis earlier, and to avoid unnecessary tests and treatments. Especially in AIP, once an episode or attack starts, if the right medications/treatment are not given soon in the crises (and unsafe medications are not avoided), the consequences are devastating for the patient. Especially in my wife's case, by the time she was diagnosed with AIP, she had an extreme muscle weakness that she was completely bed ridden for many months. She had nerve damage, seizures, extreme pain, psychiatric symptoms and was on path to a respiratory failure. She was also misdiagnosed with GBS (Guillain-Barré Syndrome) and was given unnecessary antibodies and went through so many unnecessary tests. So, we strongly suggest especially ER doctors are more aware of the symptoms and the disease.
2. We wish there would have been more treatment/management options available. Currently, there are two only treatments given in the local hospitals: Carbohydrate loading and Heme. Each has their own limitations in effectiveness and side effects. Having more treatment options could be better for the patient so in case one treatment has many side effects; an alternate is available.
3. We wish there was an easier way to give the medication to patient. The current Heme treatment my wife receives requires using a port which needs to be surgically implanted. The medication is so thick that it blocks the port overtime and requires to have the port replaced every year and half.
4. We wish the existing Heme treatment was more economical as having it high price makes it so difficult to have it easily accessible for the patient. More money means many approvals before it could be accessed. In addition, having it so high price means, the drug cannot be given purely based on symptoms and PBG urine test becomes an absolute mandate which adds further potential delays.
5. It would be helpful if the drug is locally available to reduce the transit time. In my wife's case, when she was first diagnosed with AIP, the drug was to come from US which further delayed the treatment due to transit time.
6. Lastly, we wish there was a magic drug available that would cure the disease from its roots.

What are three questions you think would be most important to ask your physician when selecting a treatment option?

1. How effective is the drug?
2. How bad are the side effects?

3. How often is it required?

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**Givlaari® (Givosiran); Treatment of acute hepatic porphyria (AHP) in adults**
Name of the Patient Group	**Canadian Association for Porphyria/Association Canadienne de Porphyrie (CAP)**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The Canadian Association for Porphyria/Association Canadian de porphyrie (CAP) is a national voluntary charity registered in 2014. The mission of CAP is to deliver evidence-based information and support to patients with porphyria, their families, health care providers and the general public across Canada and to achieve standards and evidence-based comprehensive care for all people with porphyria throughout their lifespans.

The CAP is a member of the Network of Rare Blood Disorder Organizations and a founding member of the Global Porphyria Advocacy Coalition (2019). CAP board members have attended the International Congress on Porphyrins and Porphyrias since 2013.

http://canadianassociationforporphyria.ca/

2. Information Gathering

To inform this submission, the Canadian Association for Porphyria (CAP) prepared and distributed a survey to its members and contacts through email and social media for a two-week period in February, 2021. The survey consisted of a combination of closed and open-ended questions, was offered in French and English, and restricted participation to Canadian patients and caregivers who had experience with acute hepatic porphyria. A breakdown of their demographic information is as follows:

Respondents:

- Unique respondents - 26
    - Acute hepatic porphyria (AHP) patients - 22
    - Caregivers - 4

- Patient diagnoses: *The survey results are representative of the acute hepatic porphyria patient population where AIP is most frequently diagnosed, and less frequently, VP and HCP (European Porphyria Network, website)
    - Acute Intermittent Porphyria (AIP) - 20
    - Hereditary Coproporphyria (HCP) - 3
    - Variegate Porphyria (VP) - 3 .
- Sex of person with porphyria:
    - Female - 23
    - Male - 3
- Age of porphyria patient
    - 18-29 - 2
    - 30-54 - 15
    - 55-70 - 6
    - 70+ - 3
- Province of residence
    - Alberta - 10
    - British Columbia - 7
    - Ontario - 6
    - Manitoba - 2
    - Quebec - 1
- Residence:
    - Urban -19
    - Rural area - 7
- Treatment
    - Patients respondents treated with Hematin (Panhematin/Normosang) - 6

In order to include the experiences of people who had received Givlaari, the CAP requested support from the British Porphyria Association (BPA). The BPA shared the results from three interviews they had conducted with people who had received Givlaari and they have given permission for this document to be referenced for this submission.

Responses from the CAP survey, ***Canadian Patients with Acute Hepatic Porphyria (AHP) and Caregivers, 2021***, form the backbone of this submission, with interview results from the BPA survey, ***Experiences from acute porphyria patients (recurrent attacks) presented as a series of patient testimonials***, (BPA, 2020) informing the question on the drug under review. These sources echo and are supplemented by the results of an earlier CAP survey and the experience of CAP volunteers who have been supporting Canadians with porphyria since CAP was founded in 2014.

3. Disease Experience

Profile of Patient #24,
Canadian Patients with Acute Hepatic Porphyria (AHP) and Caregivers, 2021

"Living with porphyria is not really living at all"

Respondent #24 is a woman, aged 30-54 with Hereditary Coproporphyria. She experiences porphyria symptoms, including pain, fatigue, muscle weakness, anxiety and depression, on a daily basis. She must spend most of her time at home and in a dark room to manage symptoms and minimize attack triggers. As a result she is unable to work, is isolated from her community and relies on her partner to care for their children. She has frequent acute attacks and has been hospitalized more than 10 times in the past year. In some of her visits to the emergency department, her porphyria has been dismissed or disregarded, leading to delays in accessing necessary treatment. As a result of her experiences in the emergency department, she has been diagnosed with PTSD. She has also begun to experience complications from treatments and from acute hepatic porphyria- including vision loss due to high blood pressure, nerve damage in her hands, and iron overload due to frequent hematin infusions.

Acute Porphyria Attacks

"It has been my worst year ever. [An attack will] last for around 2 weeks goes away and comes back in around again in 3 to 4 weeks." (#8)

"There have been periods of time where she had two attacks per month that required an ambulance call & hospitalization, this went on for about 6 months, then attacks were one each month and if she's lucky she can go two months without an attack. Each one is horrendous & drains her of the limited energy she has." (#11)

"I've watched her lose the use of her legs from paralysis, convulse with seizures and scream in pain." (#11)

The acute hepatic porphyrias are typically described as acute, intermittent disorders, characterized by attacks where the patient will experience intense abdominal pain, and may experience seizures (as 18% of AHP patient respondents had), paralysis/nerve damage/neuropathy (as 95% of AHP patient respondents had), requiring hospitalization and care in an ICU. Without intervention, the damage from these attacks can be permanent. In the open-ended questions respondents identified the lasting damage attacks had done: atrophied limbs necessitating use of braces and wheelchairs, and the loss of organ function.

Frequency of attacks varies: 86% of AHP patients reported having at least one attack in the previous year, and 36% reported 10 or more. For those with recurrent attacks, they were often associated with menstrual cycles, and several described it as "riding a wave" or as an unending cycle. It was noted by several of the older respondents that their attacks and symptoms lessened only with menopause.

While the distinction between an acute attack and more chronic acute hepatic porphyria symptoms isn't always clear, severe attacks require hospitalization (Stein et al., 2013). Frequency of severe attacks that require a hospital visit can vary considerably from patient to patient, with 55% of AHP patient respondents reporting that they had gone to the emergency room at least once in the past year, and 18% reporting going more than 10 times. In addition, 36% of AHP patients reported being hospitalized at least once during the year, and 9% reported being hospitalized 10 or more times in the past year.

Negative Hospital Experiences

"Because some of the doctors who don't understand porphyria think that I'm a drug seeker and refuse treatment, sometimes for days. These incidents have been traumatic for me and as a result I also now suffer from PTSD." (#24)

"I broke my hip and was given the wrong anaesthetic when surgery was done . The hospital unit I was on did not begin to treat the porphyria symptoms until I had spent 12 days there. It seemed no one cared that I had porphyria--they only saw me as a hip surgery patient done." (#25)

A significant finding of the survey was that the hospital is not perceived as a safe place for patients with acute hepatic porphyria, several (23%, n=6) respondents noting in the open-ended questions that because of past experiences they were reluctant to access medical care. In the survey and anecdotally, many AHP patients report delays in receiving appropriate care because medical professionals either do not believe the patient or are unaware of how to appropriately treat porphyria. These delays and administration of unsafe drugs can exacerbate the attacks and increase the risk of permanent damage to limbs and organs.

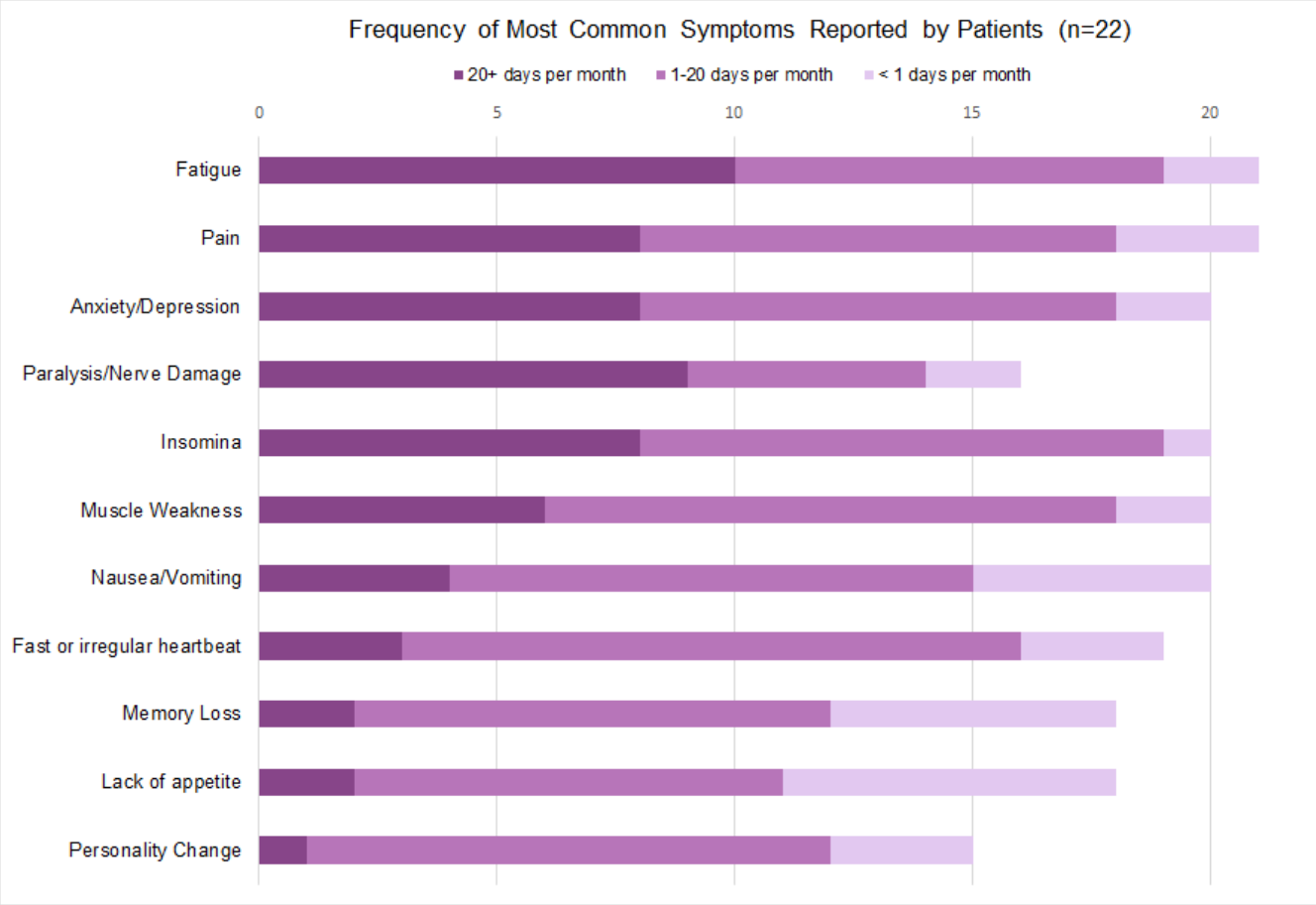
Day-to-Day Disease Experience

There are days when I can't function because of the pain. I have to stay in bed...The pain and extreme fatigue are the hardest to deal with...there are moments when the attacks got so bad- abdominal pain that made me vomit, not being able to eat, having diarrhea and anxiety all at the same time- that I just wanted to die...Not because I don't like my life, but because it had become unsustainable and unbearable." (#15)

"[I] can't walk at times, have to crawl. Very, very frustrating, just sick of being sick." (#8)

"I'm incapacitated half the time. The other half is in slow recovery." (#6)

It is important to emphasize that while porphyria is characterized as being intermittent and acute, many patients with AHP experience the disorder as an unrelenting series of attacks and slow recovery. For example, more than 80% of AHP patient respondents reported experiencing the most common symptoms identified in the survey (pain, fatigue, anxiety/depression, muscle weakness and insomnia) at least once a month, and a substantial minority of respondents (27-45%, depending on the symptom) reported experiencing these symptoms more than 20 days per month. A breakdown of the most commonly experienced symptoms is as follows:



Long Term Health Complications

"Permanent damage from initial flare left me in a wheelchair with atrophied hands." (#26)

"I have lost all major organs but 1 foot of large bowel, a little of small is left, all organs but heart, lungs, and liver." (#2)

In open-ended responses, many respondents reported long-term complications due to porphyria or the treatments that impacted their health and quality of life, including: experiencing vision loss and kidney disease, accumulating nerve damage resulting in atrophied limbs and organ damage, and diabetes resulting from high sugar diets.

Impacts of Porphyria on Mental Health

"I don't see any hope for my future, I feel helpless….This is no way to live." (#24)

"There is a lot of grieving, loss of work, social losses and having to accept the illness…. I suffer from isolation because I have to stay inside to protect myself from the sun… The anxiety attacks and depression were intense and difficult to get through." (#15)

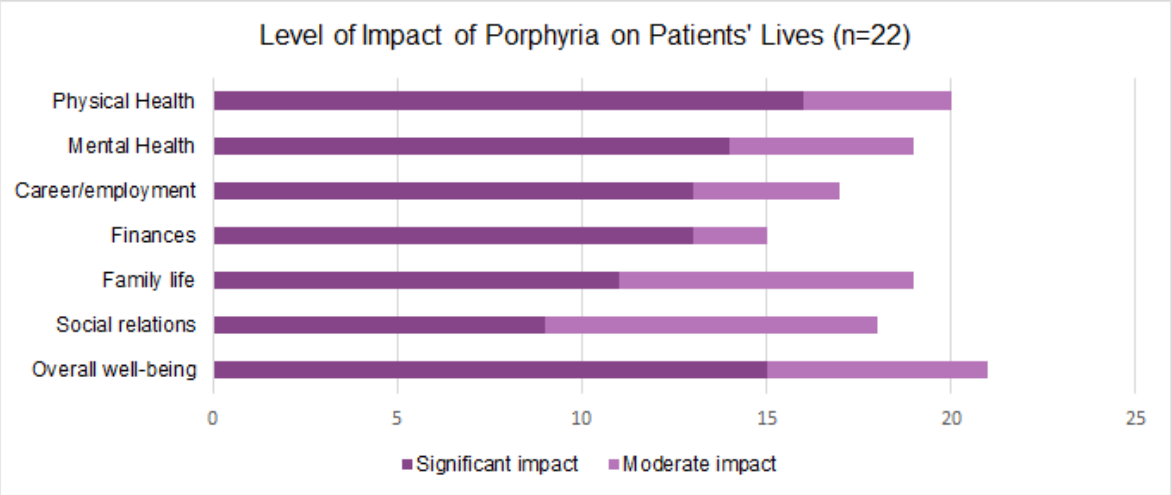
"The psychiatric symptoms are debilitating . Attacks start with a distinct foggy head difficulty processing thought, inability to make decisions, memory issues, high anxiety, restlessness withdrawal, obsessive thoughts paranoia unable to stop mind from racing causes insomnia." (#20)

In the survey, 64% of AHP patients reported that porphyria had a significant impact on their mental health. Many of the mental health impacts- anxiety, personality change and psychosis- are symptoms of porphyria itself: 82% of patients indicating they experienced anxiety or depression monthly, and 38% indicating that they experienced anxiety or depression more than 20 days per month. Antidepressants (32%) and anti-anxiety (41%) medications were among the most frequently reported treatments.

In addition to the psychiatric symptoms caused by porphyria, the experience of living with porphyria can have a profound impact on the patient's well-being. In open-ended responses, AHP patients reported depression, feelings of hopelessness, grief and isolation.

Acute Hepatic Porphyria Impact on Quality of Life for Patients and Caregivers

In the survey, both AHP patients and caregivers indicated that acute hepatic porphyria had a profound impact on all aspects or their life, including mental and physical health, career and finances, and their social and family lives. 94% of AHP patients and 100% of caregivers indicated that AHP had a significant or moderate impact on their overall well-being, with the majority of both patients and caregivers indicating that the impact had been significant.



Impacts on Finances and Career

"I haven't worked for the last 2 and a half years because of porphyria. I have been obligated to go on welfare. I'm not living on the streets but am now very low income." (#15)

"I can't work...I have limited housing options due to having to be on social assistance as well as them having to be wheelchair accessible." (#26)

"I was stretched so thin helping my daughter and working full-time that I went to part-time and then retired as I wasn't able to sustain the level of energy required to do work and be there for her in times of crisis. When I wasn't able to be there I paid someone else to be." (#11)

"I usually have to make arrangements at work on a short notice when my wife is in attack and have to take her to the hospital and have to work from hospitals many times." (#10)

"It has destroyed and robbed me of my education, livelihood, finances and health." (#2)

Acute hepatic porphyria has significant impacts on the careers and financial health of AHP patients, particularly for those with chronic symptoms or frequent attacks. In the survey, 59% reported that porphyria had a significant impact on their career, with 45% indicating in open ended questions that they had left the workforce as a result of porphyria. Being unable to work has repercussions for their financial security, with 59% of patient respondents indicating the porphyria had a significant impact on their financial well-being. In open-ended responses, respondents reported requiring government financial support including social assistance and long-term disability.

Caregivers also reported career impacts, with 50% saying the impacts had been significant. In open-ended responses, caregivers reported that they had to take time off, sometimes on short notice, and one caregiver indicated they had left the workforce.

Impacts on Family and Social Life

"Having children is a challenge for us as my wife's first attack was due to pregnancy. Maintaining social relations or going out for holidays also becomes challenging as we always have to be ready for the worst moment." (#19)

"He may as well be a single dad as I can't be involved because of my sickness." (#24)

"Due to my inability to get around easy, I no longer have a social life. I don't have any romantic relationships because it's hard to get someone who understand the nature of always being sick. I have decided to never have children, as to not pass on these genes." (#26)

"There are days when I can't function because of the pain. I have to stay in bed. I suffer from isolation because I have to stay inside to protect myself from the sun." (#15)

Of the AHP patients who responded to the survey, 50% indicated that porphyria had had a significant impact on their family life, and 41% indicated a major impact on their social life. In open-ended responses, patients indicated that pain, fatigue and frequent attacks, as well as isolating to avoid triggers, made it difficult to establish and maintain social and romantic relationships, and care for their children. Two respondents also indicated that porphyria had impacted their decision to have children- for fear that pregnancy would trigger attacks and to avoid passing on the disease.

Mental Health Impacts on Caregivers

"I am constantly exhausted. I wake feed kids take to school go to work pick up kids cook supper get kids started on homework clean house do laundry. I am overwhelmed 90% of the time. I always worry that if I get called out for work that an attack may come. I'm worried that I'll come home and she will be dead. The list goes on and on. We have very minimal relationships with any friends anymore because we have had to cancel so many times." (#23)

"Caring for someone with porphyria is extremely challenging. Seeing someone in pain all day especially when you know there is only little can be done, takes a big toll on you mentally. It affects your employment, family life and relationships with family members/friend… I always have to stay strong to support my wife and myself."(#19)

"It hurts so much to see her suffer for no reason...Emotionally it has effected our marriage and family since this disease is the only thing that is constant stress every day in either trying to find help or helping her recover from attacks." (#10)

The responses from caregivers revealed a palpable level of distress. Of the 4 caregivers who participated in the survey, 3 indicated that caregiving for someone with AHP had had a significant impact on their mental health. Caregivers described pain at seeing a loved one in pain and struggling, being overwhelmed by the care roles they took on, grief for the changes to their relationship and fear for the future.

4. Experiences With Currently Available Treatments

Patient Profiles

Canadian Patients with Acute Hepatic Porphyria (AHP) and Caregivers, 2021

Patient #24
"All of the medication that I'm on is not controlling my symptoms and I keep having attacks that require admission to the hospital. "

#24 has exhausted all the treatment options to treat porphyria: she avoids triggers by spending most of her time in a dark room, eats a high sugar diet, receives Lupron injections and regular infusions of hematin. Despite these treatments, the attacks are not under control and, as a result, she has been hospitalized more than 10 times in the previous year. The treatments, while she believes they have helped reduce the number of attacks, have significant side effects including inducing menopause and causing iron overload. These effects make her afraid to continue with the treatments, however she is also afraid of the consequences if they are discontinued. To manage her symptoms, she also takes opioid and non-opioid pain medication, antidepressants, anti-anxiety, sleeping and blood pressure medication.

Patient #13
"Unrelentless attacks"

#13 is male, aged 30-54 with Acute Intermittent Porphyria. As a result of previous porphyria attacks, he has lost part of his large intestine and has limited hand strength and has been on long term disability for 15 years. His attacks which cause intense pain, seizures and psychosis, are frequent. To manage his attacks he receives a weekly hematin infusion through a central line at a cancer clinic and eats a high sugar diet. While the infusions have helped, he still had more than 10 attacks each year, 2-4 of which resulted in hospitalization, and reports experiencing pain, fatigue, muscle weakness, memory loss and anxiety on a daily basis. He has also developed Type 2 diabetes as a result of his diet. To manage symptoms he also takes antidepressants, antipsychotics and non-opioid painkillers.

Acute Hepatic Porphyria Treatment

Hematin is the only treatment for acute hepatic porphyria and is intended for use during attacks (Schmitt et al., 2018). Preventing attacks is key, as once they are in progress, attacks are life threatening and can result in permanent damage to limbs and organs.

Treatment during Attack

"Being admitted to hospital to receive Panhematin & pain medication helps me get through the attacks but in spite of treating my attacks my chronic symptoms had continued to get worse." (#24, Patient who has been hospitalized more than 10 times in the past year because of attacks)

"The last 4 times they kept me in the hospital for a few weeks waiting for Panhematin….Twice they threw out a full line of Panhematin….on two separate occasions [I] received serious staph infections through IV sites... Many complications due to human error." (#4)

"Having it so high priced means the drug cannot be given purely based on symptoms and PGB urine test becomes an absolute mandate which adds further potential delays." (#19)

If a severe attack does occur, there is only one recommended treatment- hematin (Panhematin or Normosang), which helps reduce the duration and severity of the attack. Hematin is a blood product that must be delivered through a large peripheral vein or a central line, and treatment should begin immediately. In the survey, 27% of patient respondents indicated they had been treated with hematin. Treatment guidelines indicate if hematin is not immediately available, that a glucose infusion can be administered in the interim,and in the open-ended responses two respondents indicated they were still only being treated with glucose infusions.

Survey respondents reported several challenges in receiving hematin in a timely manner- it should be commenced as soon as possible after attack onset (Stein et al., 2013). Most hospitals do not have the drug on hand and have to wait for the product to be shipped; additional diagnostics are ordered before prescribing; the product being improperly handled or administered and wasted as a result; and emergency departments being unfamiliar with acute hepatic porphyria and delaying, sometimes for days, the start of treatment.

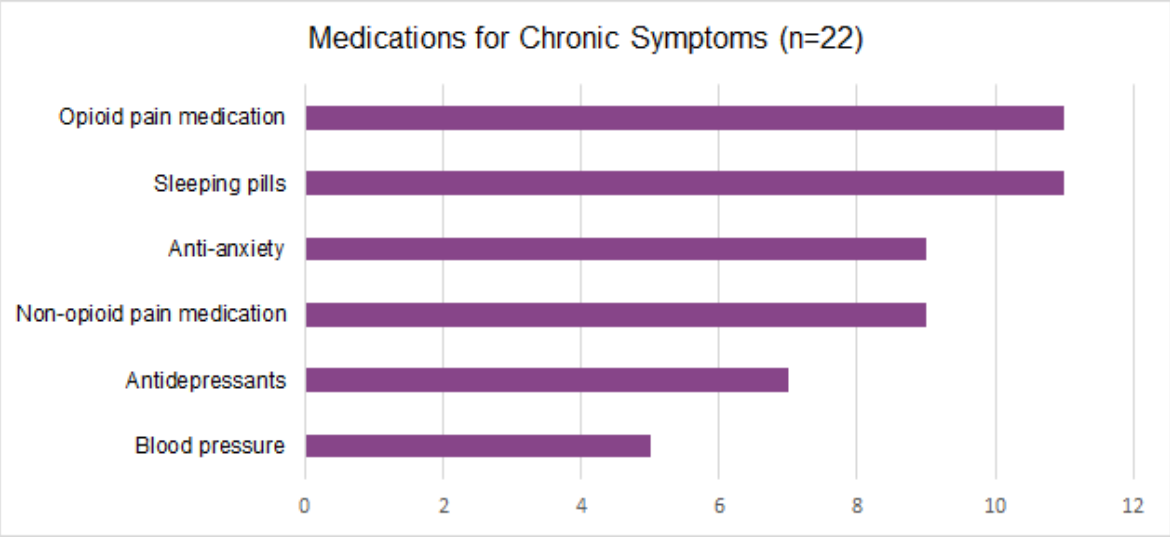
Symptom Management and Preventative Strategies

"There was a period of 1½ years where I was taking 1½ cups of sugar a day." (#20)

"Because of the dramatic swings in temperature where I live (very hot in summer & very cold in winter) this has caused me to stay indoors where I can control my environment which has isolated me from the community and the world. (#24)

"Sensitivities to the environment, foods and chemicals have been profound to the point where I lived in my environmentally safe bedroom for 7 years and was forbidden by drs to step outside." (#2)

AHP patients described the primary approach to managing acute hepatic porphyria as preventing attacks by avoiding attack triggers (86% of patient respondents) and adopting a high glucose diet (82%). Additional medications may be prescribed to manage symptoms that persist, with the most common being opioid pain medication (50%), sleeping medication (50%), non-opioid pain medication (41%), anti-anxiety medication (41%) and antidepressants (32%).



While the management approach focused on diet, avoiding triggers, and medicating for symptoms helps some AHP patients, it is not without its side effects. Survey respondents identified the following side effects:

- The long term consumption of high quantities of sugar led to weight gain and its associated complications, including Type 2 diabetes.
- Avoiding triggers, which can include stress, pharmaceutical and environmental factors, can lead to isolation, as in some cases, the only way to effectively avoid triggers is to never leave their home.
- Opioid pain medications, while safe (won't trigger an attack) to give AHP patients and effective at managing pain and not desirable as a long term solution to chronic pain.

Intractable Acute Hepatic Porphyria

"Could not achieve control with panhematin, was getting weekly treatments and needing more and more." (#13, Patient had more than 10 attacks, and was hospitalized 2-4 times in the previous year)

"They manage the acute attack but the chronic pain and symptoms between have gotten worse. The need for so many hematin treatments raised her iron levels to 15 times the normal limit which made her even sicker." (#11, Parent of patient who was hospitalized more than 10 times in previous year)

"My daughter is on her 6th port and they are running out of places to put subsequent ports when this one fails. This is a big worry as without a port she can't get treatment. Her ports have lasted anywhere from 6 months (infection required replacement) to a year." (#11)

"The medication is so thick that it blocks the port overtime and requires to have the port replaced every year and half." (#19, Spouse of patient hospitalized more than 10 times in previous year)

If avoiding triggers and managing acute hepatic porphyria through diet does not eliminate attacks, there are limited options available:

Gonadotropin-releasing hormone (GnRH) analogues

For women whose attacks are triggered by hormonal changes in their menstrual cycle, regular injections can induce menopause and can reduce the frequency of attacks. In the survey, two patients (9%) indicated they were being treated with Lupron. They indicated varying levels of effectiveness of this treatment- attacks were not eliminated but respondents believed it had reduced the number, though efficacy seemed to decline over time. Respondents also indicated serious concerns about the side effects of long term use of these drugs, including osteopenia, and both indicated they did not want to continue taking the drug due to its side effects but were afraid of increased attacks if they stopped this drug.

Prophylactic hematin

For AHP patients with frequent attacks, regular infusions of hematin can be administered as a preventative measure. Survey respondents identified several major challenges to using hematin as a preventative treatment:

- Hematin is an irritant to veins and can lead to the loss of the superficial venous system (Stein et al., 2013). It must therefore be administered through a central line, and ports must be replaced regularly. Once port locations are exhausted, hematin is no longer a treatment option- either for acute attacks or as prophylaxis.
- Regular treatment with hematin can lead to iron overload and require phlebotomies.
- If hematin treatments cause blood clots it must be discontinued.
- Patients must travel to a hospital or cancer clinic in order to receive treatment, creating a barrier to access.
- In addition to the side effects and challenges with administering the drug, use of hematin does not fully prevent attacks or eliminate symptoms, and potentially contributes to the prolonged recurrence of attacks (Schmitt et al., 2018). This means that while severe attacks are reduced, the patient continues to experience chronic symptoms including pain, nausea, fatigue and muscle weakness.

Liver Transplant

If acute hepatic porphyria is still not under control once the above measures have been exhausted, a liver transplant is the last resort (Stein et al, 2013).

5. Improved Outcomes

AHP symptoms can be life-threatening. AHP symptoms can be chronic and life-limiting. Current treatments (such as hematin) reduce the length and/or severity of intermittent attacks. Treatment with Givlaari has been shown to reduce or eliminate intermittent attacks and reduce the ongoing, relentless, chronic symptoms that many AHP patients experience.

Profile of Patient #24,
Canadian Patients with Acute Hepatic Porphyria (AHP) and Caregivers, 2021

"If I could eliminate attacks and be less sick all of the time I would maybe have a chance of getting a life back."

For #24, unmanageable porphyria attacks and treatment side effects have meant that she is bedridden and in pain much of the time. She is unable to work or participate fully in family life. She has exhausted the available treatment options, and while she believes the frequency of attacks is less, she has still been hospitalized more than 10 times in the last year due to attacks. The available treatment options may not be viable much longer: her iron levels are dangerously high and require phlebotomy to address, and she is running out of sites for a central line. She takes many additional medications, including opioid pain relief to manage the symptoms and side effects.

For #24, a better outcome would include: a treatment that more effectively prevents attacks, doesn't require central line access, has options for access outside of the hospital, reduces the chronic symptoms, has less side effects, and allows her to participate more fully in parenting and family life.

Improved Outcomes

The responses from survey participants about what they would like to see from a acute hepatic porphyria treatment, echoed many of the themes identified by # 24 in the case study.

Prevent AHP Attacks

"Give treatment to avoid attacks not after the attack is so severe."(#9)

Both patients and caregivers discussed the importance of preventing attacks. AHP attacks are episodic, necessitate hospitalization, can cause permanent damage to organs and limbs, and require a long recovery period. Currently hematin is used to reduce the severity of attacks, but, because of its side effects and difficulties with administering it, it is not a long-term prophylactic solution. Other preventative measures (sugar diet, avoiding triggers through isolation, GnRH analogues) are limited in scope and, if inadequate, AHP patients have no other treatment options.

Reduce Chronic AHP Symptoms

"My life would be full again if I could become employable once more. Not only financially but mentally to be a functioning member of society." (#7)

"If I could reduce the number of medications I need to use I'd be grateful."(#24)

As discussed above, many AHP patients experience debilitating chronic symptoms including chronic pain, overwhelming fatigue, muscle weakness or paralysis, anxiety and depression. These symptoms are managed through taking multiple medications, including opioid pain medication, and bed rest. While these medications help, the chronic AHP symptoms can still be debilitating, and as a result, many AHP patients are unable to work, maintain relationships or participate in family life. Ideally, AHP patients would like a treatment option that prevented attacks and reduced chronic symptoms. As discussed in the "Experience with Currently Available Treatments" section, prophylactic hematin, while it reduces the severity and frequency of attacks, can worsen chronic symptoms.

More Accessible

"Not having to go through ER each time and wait in queue for Pan Hematin." (#4)

"I would like to see treatment available in every hospital for easy access for all."(#7)

I would like not to require venous access (#15)

"We wish there was an easier way to give the medication to patient. The current Heme treatment my wife receives requires to use a port which needs to be surgically implanted... and requires to have the port replaced every year and half." (#19)

Respondents identified several barriers to receiving treatment including physical barriers (62%) like requiring venous access and side effects, having to travel to receive treatment (31%), lack of access to knowledgeable medical professionals (73%) and cost (31%). In open-ended responses, respondents discussed:

- The importance of *not* having to visit the emergency department to receive treatment. Respondents described having to fight for needed treatments in the ED. There are often delays in treatment because they are viewed as drug seeking, staff are unfamiliar with their care needs, or because some patients are told that hematin is expensive and so additional diagnostics required (note: hematin is now available through Canadian Blood Services w/o additional cost to patient, hospital or province. Some respondents may not have known this.)
- Concerns about requiring central lines and running out of ports. The administration of Hematin requires patients to visit a hospital or cancer clinic for administration. The ports to deliver the medication must be replaced regularly (6 months to 1.5 years).

For respondents, more accessible treatments are those that could be delivered orally or through subcutaneous injection, and could be administered in a community clinic or at home.

More Options, Less Side Effects

"I've stopped thinking of ways to make my life better because nothing seems to work." (#24)

Currently, there are two only treatments given in the local hospitals: Carbohydrate loading and Heme. Each has their own limitations in effectiveness and side effects. Having more treatment options could be better for the patient so in case one treatment has many side effects; an alternate is available. (#19)

Respondents discussed the limited treatment options available, and several indicated that the primary treatment available to them, hematin, had either been discontinued or would no longer be viable due to side effects and complications (blood clots, iron overload, loss of ports). Having more treatments would increase the likelihood that there would be a treatment option that would work for each patient and avoid the need to consider a liver transplant.

Summary: Benefits of Desired Outcomes

"Treatment that works would allow her to be a mother again a wife again a friend again. This would be incredible to see and have the women back that we had 10 yrs ago. I honestly don't even know what or how it would change life because it's been so long not having her." (#23)

"If I could eliminate attacks and be less sick all of the time I would maybe have a chance of getting a life back." (#24)

AHP patients and caregivers discussed that a treatment that prevented attacks, reduced chronic symptoms, and was more accessible to patients would be life changing. They indicated that if their acute hepatic porphyria was better controlled, they would be able to participate more in their community and family, return to work, and reduce the number of medications for side effects (particularly opioids). Moreover, preventing attacks would reduce the number of hospitalizations, the risk of permanent neurological damage, and the need for ports and travel for Hematin.

6. Experience With Drug Under Review

Treatment with Givlaari - Patient experiences

> *"Two years on Givosiran (ENVISION trial) - completely life-changing experience."*
> Patient F, Acute Hepatic Porphyria Patient Testimonials, British Porphyria Association

> *"Finally, in my mid-40s, Givosiran has given me the chance to start experiencing life as it should be."*
> Patient A, Acute Hepatic Porphyria Patient Testimonials, British Porphyria Association

> *"Now age 27, Givosiran for two years as part of ENVISION - completely life-changing effects*"
> Patient C, Acute Hepatic Porphyria Patient Testimonials, British Porphyria Association

No Canadians on Givlaari responded to the CAP 2021 survey so we turned to the British Porphyria Association who generously shared the outcomes of three AHP patients using Givlaari . **All three described the treatment of Givlaarii as life-changing.** Profiles of the three patients can be found on the following pages.

Summary- Benefits of Givlaari

Impact on Day-to-Day Life

- reduced or eliminated attacks
- reduced or eliminated pain and pain medications
- improved appetite/digestion
- improved strength, mobility, energy, and general physical health
- reduced fatigue
- improved sleep
- improved concentration
- reduced nausea
- reduced anxiety

Impact on Family Life

- improved independence
- decreased reliance on others for support
- life is described as normal (marriage, being a mum, contributing to family life)

Impact on Work

- increased work hours
- improved employment, career opportunities and study
- able to contribute to family finances

Patient A

Background and management

Diagnosed aged 19 after a series of severe attacks. Years of recurrent life-threatening paralysing attacks (worst between ages 19 to 26). Hospitalised for at least two weeks out of every month, as well as numerous ICU admissions and an 18-month admission where recovery looked uncertain.

Treatments: Weekly haem arginate for more than 16 years (first as an in-patient, then out-patient, then self-administered at home). Tried GnRH: worked for 6 months before attacks re-started. Started Phase I/II trial of Givosiran in 2016.

Complications: Damaged veins / sixth portacath. Severe nerve damage and muscle wasting. Renal impairment. Assessed for joint liver/kidney transplant 2015-16 due to lack of treatment options.

Impact on day-to-day life

Haem arginate	Givosiran
• Horrific pain on a daily basis – years on pain relief • Constant nausea and lack of appetite • Repeated bouts of paralysis – never got chance to recover from one bout before another added to it • Mobility and ability to self-care severely impaired – wheelchair and sticks used but still had regular falls and injuries • Constant planning, administering and recovering from haem treatments	• No attacks and no pain • Appetite returned • Digestion improved due to not using opiates • After prolonged period with no attacks, improvements in mobility and nerve damage • Improvements to physical strength and fatigue • Givosiran monthly injection easier and less time-consuming to administer and manage, plus no recovery time needed

AIP robbed me of so much: to take part in normal life, the chance to work and develop a career, to have another child, to walk, run and exercise, to travel. Finally, in my mid-40s, Givosiran has given me the chance to start experiencing life as it should be.

Impact on work, study and finance

• Working full time until first bad attacks • Unable to work at all for around 8 years • Eventually became self-employed (a few hours a week) as unable to commit to a regular part-time job due to pain, fatigue, unpredictability of attacks (incl. hospital admissions) and time-consuming treatments • No opportunity to develop a career, buy own home or plan for future financial stability	• Able to plan when treatments are needed • No attacks and no opiate-based pain relief has improved concentration and physical health • Able to increase amount of hours worked and take on regular employment • Now have the potential to plan for a slightly more secure future

Impact on family, social life and relationships

• Periods of complete dependence on partner and family for physical care as well as financial support	• Much valued independence and reduced reliance on others for support

Most of my twenties disappeared in a blurry haze of hospital admissions and all that comes with them – pain, sickness, endless puncturing from needles, total paralysis, breathing assistance, humiliation of being unable to care for personal needs or feed self, haem, more haem, sickness, pain, PAIN, PAIN! And repeat!

Patient C

Background and management

Diagnosed aged 10, recurrent attacks for many years, and weekly haem arginate from age 13

Life-threatening attacks with pain, sickness, paralysis and severe hypertension (200/140 @ age 10)

Complications: numerous portacaths & PICC lines with extremely poor venous access, iron overload (treated with medication); haem arginate gradually stopping being effective, despite increased dosage

Assessed for liver transplant due to lack of available treatment options

Now age 27, Givosiran for two years as part of ENVISION – completely life-changing effects

Haem arginate

Givosiran

Impact on day-to-day life

- Constant fatigue
- Pain in legs, abdomen, back and chest
- Constant nausea and lack of appetite
- Extreme weakness and nerve damage
- Restrictions on ability to travel due to reliance on haem. No trips abroad
- Unable to do any form of physical exercise or sport
- Huge amounts of time planning due to constant treatment and recovery making it difficult to juggle any form of normal life

- More energy and active
- No longer in pain all the time
- Low impact of Givosiran injection in terms of tiredness and strain on body
- Able to travel abroad for the first time since starting on the trial
- No need to prepare for haem – convenient to administer
- Portacath removed after several years
- Able to take driving lessons

Impact on work, study and finance

- Ages 10 to 17, school attendance was only between 9% and 21% due to hospitalised attacks every 6-7 days (4 haem treatments)
- Delayed university, graduated later than expected
- Missed opportunities & career goals

- Able to make career plans
- Time and energy to dedicate to studies
- Gained accreditation in a graduate programme since being on the trial
- Able to work and earn a salary

Impact on family, social life and relationships

- Was in a relationship but was reluctant to commit when future was so uncertain
- Felt like a burden – disheartened/depressed
- Quiet and kept to self without much interaction
- Parents constantly worrying

- Able to live a relatively normal life
- Recently married and optimistic about future
- No longer dependent on others
- Able to participate in sports and hobbies
- More social and outgoing

Other impacts

Brother started with attacks aged 19/20. Now 30, he is suffering the severe mental impact of regular attacks. He is currently being treated with Haem every 7-10 days. Used to be a very social and outgoing person, but now constantly in pain and unable to work or study. He is depressed and feels trapped at home for the last several years without any sign of improvement.

"Givosiran gave me faith that miracles really do happen and that there is hope to live a somewhat normal life, and everyone deserves that chance!"

Patient F

Background and management

Started with symptoms age 27, pain in back, stomach and legs escalated quickly into first attacks.

Rapidly deteriorated to recurrent attacks associated with monthly hormonal fluctuations. Monthly hospital admissions for 6 months with 4 doses of haem each time.

GnRH failed to suppress hormones - attacks continued - but with the addition of 'unbearable' side effects.

Regular haem therapy started monthly, then fortnightly as an out-patient, then weekly via homecare.

Two years on Givosiran (ENVISION trial) – completely life-changing experience.

Haem arginate	Givosiran
Impact on day-to-day life	
• Dependent on a concoction of pain relief medications/approaches to deal with chronic pain • Constantly nauseous • Insomnia and disturbed sleep • Huge anxiety made worse by pain and medications	• No regular pain relief – bowels better as not using opiates • Not sick and nauseous • Sleep pattern has normalised • Reduced anxiety
Impact on work, study, finance and relationships	
• Prior successful career (full time) in training/HR • After attacks started, increased absenteeism from work – functioning <50%, then part-time hours • Made redundant within 7 months of attacks starting • Unable to work for at least a year • Husband took sole financial responsibility as well as helping with personal care • Unable to fully care for daughter when first born	• Able to begin working more hours • Able to plan and adhere to a regular work schedule • Potential to develop a career • Increased independence and the potential for financial input into the relationship • Able to fully contribute to family life and enjoy being a mum

I suffered a progressive deterioration in health with each attack: increased weakness, more pain, more fatigue, disturbed sleep, more haem, more sickness, more use of the wheelchair, escalating levels of medications, anxiety around earnings, lost independence, lost job and company car, downsized home as couldn't afford on one wage, complete dependence on partner for physical care, such as bathing, cooking and cleaning, as well as complete financial dependence on my partner and the benefit system. Administration of the haem was so stressful; none of the nursing staff knew what they were doing – it was terrifying as I didn't know what to do either. One of the hardest things was also having to admit that I couldn't do things that I was previously able to do.

Givosiran has been completely life-changing. I am able to contribute to family life, to my life, to think of the future. I feel able to take on responsibilities as a mother, a wife, and an employee – as everyone should be able to! I don't have to continuously plan. I'm able to live a life that I did before …. and for the first time in a long time … I'm excited for what my future could be again.

7. Companion Diagnostic Test

The CAP is unaware of any companion tests.

8. Anything Else?

The needs of Acute Hepatic Porphyria patients are not being met.

Acute Hepatic Porphyria symptoms can be life-threatening. Acute Hepatic Porphyria symptoms can be chronic and life-limiting. Current treatments (such as hematin) reduce the length and/or severity of intermittent attacks. Treatment with Givlaari has been shown to reduce or eliminate intermittent attacks and reduce the ongoing, relentless, chronic symptoms that many AHP patients experience.

Given that Givosiran has been demonstrated to be "completely life-changing" (BPA, 2020) and has the potential to improve the lives of so many AHP patients, what might limit the CADTH recommendation for Givosiran?

Thapar, et al., 2021, in their paper, *Givosiran, a novel treatment for acute hepatic porphyrias,* conclude the following:

> *"Givosiran is expensive, and few patients, especially those suffering from symptomatic AHP, who usually are unemployed or under-employed, will be unable to afford it's high monthly cost. Thus, it seems likely that insurers and national health care systems will restrict their support for its use to patients with well-diagnosed AHP and with recurrent and ongoing frequent acute attacks. One reasonable stance would be to approve reimbursement for the drug only for patients who, in the prior 6 months have had at least two acute attacks that were severe enough for them to require hospital admission and/or multi-day courses of IV heme. Those who have developed adverse side-effects from heme, such as headaches, muscle aches, evidence of oxidative stress and pro-inflammatory syndromes, should also be considered for a trial of givosiran, as should patients with evidence of primary or secondary iron overload, in whom further heme therapy is risky and relatively, if not absolutely, contra-indicated."*

Overview of Recommendations for Givosiran - Thapar, Rudnick & Bonkovsky, 2021
Givosiran should be reimbursed for: ● Patients with well-diagnosed AHP ● AHP patients with recurrent and ongoing frequent acute attacks ● AHP patients who, in the prior 6 months have had at least two acute attacks that were severe enough for them to require hospital admission and/or multi-day courses of IV heme ● AHP patients with adverse side-effects from heme, such as headaches, muscle aches, evidence of oxidative stress and pro-inflammatory syndromes ● AHP patients with primary or secondary iron overload

Additional Considerations for Givosiran- CAP Patient Survey, 2021

The inclusion criteria suggested by Thapar et al (2021) generally align with the findings of our survey. Based on the responses from AHP patients and caregivers, CAP suggests additional inclusion criteria for Givosiran reimbursement:

Additional Considerations for Recommendations for Givosiran - CAP Patient Survey, 2021
• AHP patients who are hospitalized or have received urgent medical care at the emergency room • AHP patients with physical challenges receiving haem treatment (ie.access to ports; venous problems, blood clots) • AHP patients with neuromuscular symptoms (such as paralysis, wheelchair use, inability to walk) • AHP patients using opioid medication for significant symptoms • AHP patients who are newly diagnosed and have significant symptoms (such as neuromuscular symptoms, seizures, paralysis, frequent attacks, and severe pain)

RECOMMENDATIONS

1. **CAP recommends that Givosiran be made available to all Canadian AHP patients that meet the criteria outlined in the two tables above. Should the above recommendations be approved, we expect 5-7 of 22 patients in the 2021 CAP survey would qualify for Givosiran (Note: there is a range in the estimate of the number of patients because the CAP survey data collected for hospitalization and emergency visits was for a year not 6 months).**

2. **CAP recommends that Givosiran be made available to Canadian AHP patients as outlined in the recommendations above using a managed access approach (CORD, 2015). Alnylam currently has an Early Access Program for Givosiran for managed access which might provide a template for Canadian AHP patient access. Participating in a managed access program for Givlaari would allow access to patients while assessing the benefit from the treatment over time. This data could inform future use of Givlaari based on real-world, Canadian evidence.**

References

British Porphyria Association. (2020). Experiences from acute porphyria patients (recurrent attacks): presented as a series of patient testimonials. Unpublished document.

Canadian Association for Porphyria. (2021). Canadian Patients with Acute Hepatic Porphyria (AHP) and Caregivers Survey. Unpublished raw data. This data may be made available upon request.

Canadian Organization for Rare Disorders (CORD). (2015). CORD: Assuring Affordability and Sustainable Access to Orphan Drugs.
https://www.raredisorders.ca/sustainable-of-access-to-orphan-drugs

European Porphyria Network. https://porphyria.eu/en/content/porphyrias

Schmitt, C., Lenglet, H., Yu, A., Delaby, C., Benecke, A., Lefebvre, T., Letteron, P., Paradis, V., Wahlin, S., Sandberg, S., Harper, P., Sardh, E., Sandvik, A. K., Hov, J. R., Aarsand, A. K., Chiche, L., Bazille, C., Scoazec, J. Y., To-Figueras, J., Carrascal, M., … Gouya, L. (2018). Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. *Journal of internal medicine*, *284*(1), 78–91. https://doi.org/10.1111/joim.12750

Stein, P., Badminton, M., Barth, J., Rees, D., & Stewart, M. F. (2013). Best practice guidelines on clinical management of acute attacks of porphyria and their complications. Annals of Clinical Biochemistry, 50(3), 217–223. https://doi.org/10.1177/0004563212474555

Thapar, M., Rudnick, S., & Bonkovsky, H.L. (2021). Givosiran, a novel treatment for acute hepatic porphyrias. Expert Review of Precision Medicine and Drug Development, 6:1, 9-18.
DOI: 10.1080/23808993.2021.1838275

Young, A., Menon, D., Street, J., Al-Hertani, W., & Stafinski, T. (2018). A checklist for managed access programs for reimbursement co-designed by Canadian patients and caregivers. Health Expectations, 21:6, 973-980.
DOI: https://doi.org/10.1111/hex.12690

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.

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

   The submission was discussed and reviewed by:

   - David Page, National Director of Health Policy, Canadian Hemophilia Society and Network of Rare Blood Disorder Organizations, Board Member
   - Silvia Marchesin, Network of Rare Blood Disorder Organizations, Board Member

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.

   No, the data collection and analysis was completed by CAP.

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
Recordati - Education Grant		X		
Alnylam - Impact for Advocacy Grant to create a Canadian Porphyria Physician Network and Treatment Guidelines				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: Wendy Sauvé
Position: President
Patient Group: Canadian Association for Porphyria/Association Canadienne de Porphyrie
Date: March 18, 2021