CADTH

CADTH Reimbursement Review

Patient Input

ravulizumab (Ultomiris)

Alexion Pharma Canada Corp.

Indication: Paroxysmal nocturnal hemoglobinuria

CADTH received patient input from:
Canadian Association of PNH Patients

August 16, 2021

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Patient Input Template

Name of the Drug and Indication	Ravulizumab for the treatment of Paroxysmal nocturnal hemoglobinuria
Name of the Patient Group	Canadian Association of PNH Patients
Author of the Submission	

1. About Your Patient Group

The Canadian Association of PNH Patients is a not-for-profit Canadian organization formed in 2009. The mission of the organization is to connect Canadians affected by Paroxysmal Nocturnal Haemoglobinuria (PNH) and advocate for the best possible care for patients and ensure they are equipped with the most current tools and information to help them live well with the condition. The organization also provides support to caregivers, and works to increase awareness and understanding of PNH.

Paroxysmal Nocturnal Haemoglobinuria is a very rare and debilitating disease of the bone marrow that affects the blood and major organs. It is a chronic, life-threatening illness and can have devastating effects upon a patient physically, mentally and emotionally. It affects 1 to 1.5 people (https://cihr-irsc.gc.ca/e/51364.html) per million. A rare disease is generally defined as one that occurs in less than 1 in 2,000 people (https://cihr-irsc.gc.ca/e/51364.html).

The organization was founded by Barry Katsof who was in need of the life sustaining medication Soliris. Eculizumab had not yet been submitted to Health Canada. He was permitted compassionate-use by the manufacturer but the medication was not allowed in through the Special Access Program.

He realized that there was no one who advocated for individuals with PNH in situations especially in such as the one he found himself in. Through self-advocacy he succeeded in securing access to Eculizumab. However, it was clear that an organization needed to be established to advocate and support individuals with PNH. Our website is: http://www.pnhca.org

Barry Katsof is also a founding member of the PNH Global Alliance (GA). The GA is an international association of PNH patients across England (Wales and Northern Ireland), Canada, Germany (two groups), Russia, Spain, the United States and The Netherlands. Barry currently is on the board of director and serve as an executive. Our website is: https://pnhglobalalliance.org/

2. Information Gathering

The Canadian Association of PNH Patients gathered information for this submission through one-on-one interviews with individuals living with PNH who live in Canada. We cite the scientific literature and other published studies on ravulizumab (hereinafter called Ultomiris) and its impacts. Many patients over the years have reached out to us proactively to learn more about the Canadian Association of PNH Patients and what we do, and how and when they could potentially gain access to ravulizumab.

3. Disease Experience

PNH is an ultra-rare blood disorder in which chronic and uncontrolled activation of complement results in hemolysis. This ultra-rare blood disorder is progressive, debilitating, and life-threatening characterized by complement-mediated hemolysis (destruction of red blood cells).[1] PNH can strike any individuals (men and women) of all races, and ages without warning, with an average age of onset in the early 30s.[2] Approximately 10 percent of all patients first develop symptoms at 21 years of age or younger.[3] PNH develops without warning and can occur in men and women of all races, backgrounds and ages. PNH often goes unrecognized, with delays in diagnosis ranging from one to more than 10 years.[4] In the period of time before Soliris was available, it had been estimated that approximately one-third of patients with PNH did not survive more than five years from the time of diagnosis.[5] PNH has been identified more commonly among patients with disorders of the bone marrow, including aplastic anemia and myelodysplastic syndromes.[6] In patients with thrombosis of unknown origin, PNH may be an underlying cause.[7]

Patients with PNH may experience a wide range of signs and symptoms, such as fatigue, difficulty swallowing, pulmonary hypertension, chronic kidney disease, shortness of breath, abdominal pain, thrombosis, erectile dysfunction, dark-colored urine, and anemia.[8]

The most devastating consequence of hemolysis in PNH is thrombosis, which can damage organs and cause premature death.[9] Thrombosis can occur in blood vessels throughout the body, and the first thrombotic event can be fatal.[10] Additionally, patients with PNH often suffer from impaired health-related quality of life.[11]

Thanks to significant progress in treatment and care, the majority of children living with PNH will reach adulthood. As the disease advances, even more time and effort are needed to manage the progressive and debilitating symptoms. Children

with PNH may need to quit school or go part-time, adults with PNH may need to leave the work force or undertake part-time work, as may caregivers of children and adults with PNH.

> *When I was first diagnosed with PNH, the doctor told me I was going to die and told my husband he needed to plan funerals. After more research and treatments I survived but I was still dependant on weekly blood transfusions. I had to quit my job and my husband took a leave of absence from his work because he had to bring me to so many clinic appointments and it was overwhelming. It is a full-time job keep me healthy. From frequent clinic visits, blood transfusions, hospital stays, and on top of that ensuring we are parenting our children…. – PNH patient, Canada*

> *After years of managing my symptoms as best I could with blood transfusions and periodic hospitalizations I then learned about an investigational therapy that was undergoing clinical trials, ravulizumab. Unfortunately I could not get on the trial because they had reached maximum capacity to enrolled. Despite being on Soliris, I am waiting to gain access to ravulizumab. I understand this drug is approved in so many other countries and looking at our friends across the border, patients are sharing how soon after starting on ravulizumab symptoms improved and I want that for myself. I want to have the liberty of having a good quality of life which means receiving the infusion every 8 weeks as opposed of 2 weeks. Especially now with the pandemic you realize what is good and what would be good for your well-being and mental health, and for me and my family we want to travel. Soliris is a burden because it keeps me here in Canada, and cannot travel with it. It is not only a lifestyle issue but a quality of life issue. I should be empowered to book travels and make memories with my love ones instead of being bound at home until my next infusion. I have one life and want to live it to the fullest" – PNH patient, Canada*

4. Experiences With Currently Available Treatments

Currently the available treatment in Canada is the first generation, eculizumab, and ravulizumab would make the second generation approved. These molecules are directed at the specific symptoms that are present in each individual. In 2009, Canada's national healthcare regulatory agency, Health Canada, approved the use of eculizumab for the treatment of patients with PNH in Canada. More than ten (10) years later patients are still fighting their public and private payers in order to gain access to eculizumab, and some patients still experience challenges accessing this life-saving treatment. As mentioned above, eculizumab is the first

drug to be approved for this disorder. It does not cure PNH but halts the breakdown of red blood cells and can reduce the risk of thrombosis and improve overall quality of life. This molecule works by blocking the complement system of the body that inadvertently destroys PNH red blood cells.

The financial cost of eculizumab for PNH has yet been successfully negotiated by all provinces/territories. One of the biggest challenges patients with PNH face is securing publicly-funded access to this life-saving treatment, and such experience is extremely traumatic, difficult and unnecessary, because in the end, deals should be struck to ensure affordability and patients access life-saving medicines. Too many Canadians with PNH have lost their lives (because of life lost is too much) while waiting for government agencies to make key evaluations and decisions, and it is this trauma that has marked much of our collective experience with current treatments.

In 2018, the FDA approved ravulizumab for treatment of the hemolysis of PNH. Since then, ravulizumab has quickly become the standard of care in the United States and elsewhere in the world. Patients here in Canada are waiting for this therapy to get reimbursed, especially in the context of the pandemic. Speaking with these patients, who are already immunocompromised, we realized they would be prefer having the option of selecting a safe option of going to the clinic every eight (8) weeks as opposed of every two (2) weeks.

Ravulizumab works in a manner identical to eculizumab, and was shown to be clinically non-inferior to eculizumab. According to ALXN1210-PNH-302 study, ravulizumab administered every eight (8) weeks for up to fifty-two (52) weeks demonstrated durable efficacy and was well tolerated, with complete and sustained free C5 inhibition[12].

We value the importance of the manufacturer's submission, as we understand not only from the ALXN1210-PNH-302 study but from patients testimonial and real life experience that although eculizumab therapy is highly effective, up to 27% of eculizumab-treated patients may experience breakthrough hemolysis,[13] resulting in a return of PNH symptoms and increased risk of serious complications. In addition, the treatment burden associated with an every-two (2) week dosing regimen of an IV infusion may negatively impact quality of life.[14]
Furthermore, the study demonstrated that patients with PNH may be safely and effectively switched from eculizumab to ravulizumab while maintaining the high level of efficacy, safety, and quality of life previously achieved with eculizumab. We believe this data should be considered during this review, as we do expect a large number of patients will want to switch to ravulizumab once it is reimbursed by provinces and private payers. According to patients testimonials, these patients want to have options and if the 8-week infusion works best for their lifestyle then they should be in a position to choose this treatment. For all efficacy end points, ravulizumab achieved noninferiority compared with eculizumab. The complete and

sustained C5 inhibition associated with ravulizumab may account for the consistent results across end points[15]. For stable patients receiving label-dose eculizumab therapy, providing an effective treatment duration that is 4 times longer between infusions by switching to ravulizumab given every 8 weeks is likely to result in a substantially reduced burden of treatment, fewer occurrences of breakthrough hemolysis and their clinical consequences, better quality of life, and greater likelihood of retention on long-term therapy[16].

5. Improved Outcomes

According to the patients we interviewed in the context of this submission, they individually described the feeling of having the opportunity to gain access to innovative treatment. It is imperative that the decision, whether or not a medication is provided, be between a doctor and their patient. A treating physician and the patient must ultimately decide what should be the best treatment regime for the patient. These clinical benefits have massive and positive impacts on patients and their entire family ecosystem, and this cannot be overstated. There is generally a feeling of wellness, well-being which can be felt as an increase of energy once a patient commences these treatments.

There are also economic interests. In many cases, when patients are accessing treatment especially early (i.e. they are able to benefit at maximum from the treatment, they experience less organs damage etc.) they are able to get back to work or create jobs. This means a significant impact within the Canadian economy, and these patients ultimately become a lesser burden on the healthcare system. It should be as equally important for the reviewers and government to acknowledge and value this submission and potential positive impact on our Canadian PNH patients. It is vital that we get as many people back on to the ice and contributing in this life. To be successful in this, when the private sector cannot cover an individual, the province must step in. Each patients' life matters and provinces will only step in and negotiate prices if there is a positive CADTH review, and eligibility criteria that are aligned and support with clinical evidence.

6. Experience With Drug Under Review

Canadian PNH patients who have spoken with The Canadian Association of PNH Patients have described ravulizumab as nothing short of game-changing and revolutionary. It is the difference between living a full life, resuming work/creating jobs, being part of the society and improving the life and outcomes of patients. As people engage again in life, they work and create wealth and then pay taxes. They also engage in the business of life which is helping the least fortunate amongst us.

7. Companion Diagnostic Test

N/A

8. Anything Else?

It is imperative that this committee understand the full importance and significance of ravulizumab. In many ways, your decision on this life-saving treatment will be a referendum on CADTH itself. Understanding and looking closely at the clinical data as well as the real world evidence, this drug has had, game-changing, life-saving effects without exception across individuals with PNH around the world. Canada is firmly in one of the last countries in looking to publicly reimburse this medication.

Perhaps the most important benefit from ravulizumab is the freedom between the infusions (every 8 weeks) which allow patients to plan their life and live their fullest accordingly, which in another word ravulizumab offers extended control of their PNH symptoms between infusions. Furthermore, an additional benefit of ravulizumab is the specific target of the complement, since the underlying cause of PNH is ongoing hemolysis. Ravulizumab has been studied in the largest PNH trial to date.

A 2019 publication (Schrezenmeier, H *et al.* , 2019)[17] presents data that supports the conclusions of previous studies and the evidence that levels of LDH (a marker that measures PNH activity) stayed stable over time**,** patients had few breakthrough events (breakthrough events are defined as experiencing at least 1 new or worsening sign or symptom of hemolysis i.e. fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia). In the ALXN1210-PNH-302 study, patients who had no prior PNH treatment, 4% of patients in the ULTOMIRIS group experienced breakthrough hemolysis vs 10.7% in the eculizumab group[18]. In a clinical trial of people who had prior PNH treatment, no patients in the ULTOMIRIS group experienced breakthrough hemolysis vs 5.1% in the eculizumab group[19].

The announcement in August 2019 that ravulizumab had received Health Canada approval but had not been submitted to CADTH, caught us and a number of patients off-guard. The response of the PNH community in Canada was immediate, and visceral. We have contributed generously to the global advances in PNH treatment and care, and Canadian PNH patients felt left behind. Our collective mental health was impacted. The impact on mental health of being left behind and let-down is evident in our community. Patients typically get diagnosed with PNH years and years after the first symptom of PNH, some may never live long enough to know their diagnosis, and the community's mental health suffers precisely also because they are not able to get access to their treatment because of their provinces have not negotiated a price and therefore cannot access the treatment, and feel left behind. We believe that the collective mental health of the Canadian PNH population would suffer negative consequences as a result of a negative CADTH recommendation. It is unclear if, or how, that impact, or the impact on the mental healthcare system might be considered in the evaluation, but the negative consequences to the community would be real. Hence we are asking you to consider this submission.

Ravulizumab has received regulatory approval in 31 countries, 27 within the EMA centralized regulatory approval in addition to receiving approval in Australia, the United States, United Kingdom & Japan as a treatment for adults with PNH.

> *I am excited for there to be an option where I can feel I am getting my life back, meaning that I am not bound to go to the clinic every 2 weeks for the infusion. Thinking I could potentially get my infusion every 8 weeks would be an increase in quality of life- enjoying and planning trips to visit my family in the UK whom I have not seen in years. Currently I do not feel comfortable bringing my treatment with me when I travel because of the risk and liability, but if I was on a 8 week infusion treatment (ravulizumab) then I could travel for a longer period of time without worrying about bringing my treatment with me is inexplicable and incredible. Better overall health, less time in hospital, longer more productive life! – PNH Patient*

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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. Yes. Stephanie Hamzo (industry consultant)

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

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
Alexion Pharma Canada			X	
RA		X		
Apellis			X	
Biocryst			X	
Regeneron			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: Barry Katsof
Position: Founder and President
Patient Group: Canadian Association of PNH Patients
Date: August 12th 2021