CADTH

CADTH COMMON DRUG REVIEW

Patient Input

CYSTEAMINE BITARTRATE (PROCYSBI)

(Horizon Therapeutics Canada)

Indication: Nephropathic cystinosis

CADTH received patient input from:
Canadian Organization for Rare Disorders

August 1, 2017

CADTH

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Patient Group	Canadian Organization for Rare Disorders

1. About Your Group

The Canadian Organization for Rare Disorders is registered charity that provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD provides education and resources to patient groups to enable them to better meet their members' needs.

2. Information Gathering

The submission summarizes the feedback provided to the Canadian Organization for Rare Disorders (CORD) through several sources: written individual testimonials or submissions, individual semistructured interviews, and a survey created and administered by CORD.

The purpose of the individual interviews was to gain a rich, in-depth understanding of the experience of patients and families living with Cystinosis, their perceptions of the current therapies, and their feelings about the new therapy, Procysbi. This background knowledge was used to develop the survey that incorporated the most important aspects of the disease impact and the treatment options. The information also served as a framework for interpreting and validating responses to the survey.

The individuals interviewed came from several sources; two were already engaged with CORD, two were recommended by another parent, and two were recruited by their physician. The survey was distributed through a variety of sources: by the physicians contacted by CORD, through one patient fundraising group, through snowballing technique, and through posting in the Cystinosis Research Foundation (USA) Facebook. Several patient families had directly sent to CADTH individual testimonials and/or completed some parts of the Patient Submission Form. They were all referred to CORD by CADTH; about 80% were living in Quebec. The survey was posted on Survey Monkey from 30 June to 27 July 2017. The survey was only available in English but patients were encouraged to respond in either English or French. French responses have been translated into English when direct quotes are used.

This submission summarizes the feedback received through six individual parent interviews, five testimonials submitted by patients or parents directly to CADTH or to CORD, and 71 survey responses. The interviewees were all parents who had a child with infantile nephropathic cystinosis and the testimonials were from parents with one or more children who presumably (based on the content of their submission) had the infantile form of the condition. Of the 71 survey respondents, 46% were patients with infantile Cystinosis, 1% were diagnosed with the intermediate version and 1% with adult (benign) Cystinosis, with the remaining 51% identified as parents of a child with infantile Cystinosis. The average age of the person with Cystinosis is 15.1 years old and the range from (under) 1 year to 50 years old. About 50% were diagnosed under 15 months of age, with 41% diagnosed when they were between 15 months and six years old; another 3% were diagnosed between 6 and 18 years old. All individual participants live in Canada; among survey respondents, 62% were from Canada and 28% from the USA, with the remaining 5% elsewhere. Among the Canadians in the survey, 35% were from Alberta, 29% from Quebec, 19% from Ontario, and 16% from BC.

3. Disease Experience

Respondents were asked to describe how Cystinosis has affected their lives, as a patient or family. The feedback spoke to both the challenges with managing the disease and the challenges of the therapy, namely cysteamine, which works by eliminating the accumulated cysteine in the cells. About half of the patients represented in this submission were diagnosed between the ages of 6 and 15 months and the remaining patients around two to six years old. Parents described the onset of symptoms (vomiting, gagging, failure to feed, loss of weight, weakness) as very frightening, often starting at three to six months; however, because the disease is rare, some children were initially misdiagnosed or undiagnosed, resulting in many visits to emergency. This was more likely in cases involving older children and adults, especially when the family lives distant from a major hospital.

"When our son, now 18-years-old, was vaccinated at three months, he developed a high fever and a heart murmur but we were just sent home by the local hospital. At five months, we noticed that he had stopped growing but we were told we shouldn't be concerned. Then he began vomiting and gagging; he couldn't roll over of lift his neck. That was when we called the paediatrician [at a major hospital], where they noticed the crystals in his eyes and after a blood test was diagnosed with cystinosis."

About one-third of the patients represented are over the age of 22 years, so born prior to the time when cysteamine capsules, namely Cystagon, was approved in the USA and became an accessible form of cysteine depletion. For older adults, challenges are associated with multiple organ failure and progressive muscle deterioration. *"As an adult, I feel like a spectator of life. Muscle wasting makes it difficult to speak and communicate.... Swallowing difficulties robs me the pleasure of food…. I make use of a wheelchair…. I've given up driving…. I no longer work; my wife shoulders the immense responsibility of making ends meet. The financial concerns are an unrelenting stress, notwithstanding the small disability benefit I receive. Some days it feels like I live for the sole purpose of taking medication."*

"His education suffered as the result of his sick time away from school. My son is also hard of hearing." "Our child has never slept a more than a few hours at a time in his whole 14 years… compounding issues related to overall health and well being, ability to learn and retain information…. He has also been diagnosed with a learning disability in math, has impaired executive functioning and spatial relation skills…" "Our medicine and surgeries that exist to keep us alive make us feel like freaks and outcasts. At 27 I have yet to find a girlfriend or a stable group of friends because of my condition and the lack of confidence I have in myself in large part due to my condition."

As a result of kidney failure, some have undergone renal transplants with all of the concomitant adverse effects, onerous follow-up, and costs; of course the patient still has cystinosis.

In most cases involving younger children, a diagnosis and referral for treatment were made within a few months of the onset of symptoms. The fears about medical crises and the long-term impact of disease progression are somewhat abated although not eliminated. As expressed by one parent,

"Though we rarely deal with acute emergency situations now that he is on a well monitored regime of medication (e.g.,Cystagon) and supplements, the multitude of complications associated with his progressive disease are a constant worry - from a high risk of broken bones, to crystal build up in the cornea, to kidney failure and reduced cognitive ability, and even sterility and the list goes on..

"We also try our best with foods as he has an extremely hard time eating." "Mind numbing trying to find foods that he would eat…"

Through the survey, they were also presented with a list of symptoms or cystinosis-related events and asked to rate how much these affected them currently or in the past. Almost all of the patients

represented have the most severe form, infantile-onset Cystinosis. The symptom experienced by most patients currently is crystals in the eyes and/or photosensitivity, reported as "much or severe" by 44% and "some" by 50%. More than half also experience "muscle wasting", rated as "much" by 29% and "some" by 26%; about 10% had experience "some" loss of muscle in the past but not currently. Slightly more than half (52%) reported currently experiencing extreme thirst or urination while almost half (45%) said these had been problems in the past but not at this time. "Failure to grow or thrive" was a past (but not current) problem that was "severe" for 44% and "somewhat" for 25% of patients. This was currently experienced by about 29% of respondents, presumably reflecting the age of the patient since this symptom is common for infants and young children who have not yet received or responded adequately to therapy. This might also explain the experience of rickets or softening of the bones, experienced by more than half (23% "much) and 32% "some") in the past but not now and only 13% currently. Introduction of cysteine elimination therapy will resolve or avoid rickets altogether (35% reported no experience of rickets). In terms of feeding, another problem that may be age-related is vomiting. More than half (56%) had experienced vomiting in the past but not currently; whereas 38% reported vomiting as a current problem; only 6% had never had this problem. Difficulty in swallowing was manifest somewhat differently and appears to vary among patients. More than one-third (37%) reported this as a current issue and only 17% said swallowing was a difficulty in the past but not currently; almost half (47%) reported it had never been a problem.

In terms of secondary impacts, kidney failure was the most frequent and most severe, with nearly 40% reporting kidney failure or serious complications in the past (some necessitating kidney transplants); more than one-third (36%) saying the patient was experiencing symptoms related to kidney failure at this time. Only one-fourth (26%) said they had never had kidney failure. These statistics are very troubling; respondents said that many patients on Cystagon do develop kidney failure as early as adolescence and often by early adulthood because it is so difficult to adhere to the strict requirements of the dosing scheduling. Even small elevations of cysteine in the cells can have a tremendous impact on the kidneys and other parts of the body.

About 7% had experienced diabetes in the past and the same percentage currently. Nearly half (47%) said cystinosis was currently having a serious impact on their school or work life, with another 34% saying it had some impact. Similarly. with respect to home,

family, or social life, 58% reported the impact was currently “much” and 29% saying it was “some”; only 3% said there had been no impact.

As illustrated in the open-ended responses, cystinosis does indeed take a large toll on the entire family, with some parents reporting that it requires 24/7 vigilance. In addition to the challenges of regular clinic visits, parents were also seeking out physiotherapists to deal with weakened muscles and back pain, speech therapists, nutritionists, tutors, and psychotherapists. Families tended to become isolated emotionally and socially. Because cystinosis is a rare condition, most had no support from other families, except through social media. Finally, there was the very strict drug management schedule,

“Devastating, it has affected each and everyone of us in his immediate and extended family as well as personal friends emotionally and financially and even socially.” “Cystinosis has overtaken our lives and caused us to live one to two hours at a time, between alarms. Each time an alarm goes off it is necessary to react with medication for our son or risk permanent damage to his vital organs.” “…we have had to travel every 3 months … from small town to hospital for check ups. Father couldn’t handle it; bailed on us so I’m a single parent. I had to relocate and work 3 jobs for 23 years now.” “In the early years the extra stress was the main factor in our divorce.”

Parents also spoke about the tremendous financial burden due to direct cost of medications, supplements and other supplies, non-reimbursed costs of healthcare visits, household expenses for modifications or other repairs, and the loss of income when a parent has to reduce work hours or quit their job to provide continuous home care for a child with cystinosis, “Despite the financial assistance we had with our benefits there were still a few years without coverage for the Cystagon and eye drops. That alone was equal to our mortgage and bills at the time. The travel, eating out and parking costs. Increased water and hydro for the extra laundry... Replacing furniture and carpeting because of the many vomiting incidences. All the meds that were not covered. Diapers. Orthotics etc.”

On a day-to-day basis, however, the key challenge experienced by parents was the management of cysteamine therapy. While all respondents acknowledge the life-saving benefit of Cystagon as the standard drug therapy, the treatment regimen, administration, and “ability to take” the drug are

experienced by most as extremely challenging.

4. Experiences with Currently Available Treatments

Only 32 or the 71 respondents completed all the close-ended questions about treatment with medications or other therapeutic interventions, apparently because some respondents were not the patient or primary caregivers. Among these, bout 90% had received therapy, with the majority (50%) currently or in the past (36%) receiving Cystagon as the main therapy. For the Canadian only respondents, 69% were currently using Cystagon and 15% had used it in the past.

When presented with a list of potential symptoms experienced with Cystagon, 38% reported severe or very severe stomach problems (nausea, vomiting, pain, diarrhea) and 54% said they were moderate or mild. About 41% reported severe or very severe bad breath or skin odour and 48% said the problem was moderate or mild. About 25% said they frequently or very frequently were unable to take the total amount of the drug required, while about 50% said they were taking the required amount. About 30% said they were frequently or very frequently unable to take the drug every six hours as prescribed, while about 50% said they were able to adhere to the schedule. In terms of other “more common” side effects, between 20% and 25% of respondents experienced as severe or very severe each of the following: fever/chills, tiredness/dizziness, and decreased appetite with between 25% and 50% reporting these were not experienced with Cystagon.

In order to fully interpret these statistics, however, it is important to pay attention to the comments provided by patients’ and parents in the survey, interviews, and testimonials. Overall, respondents acknowledge the life-saving benefit of Cystagon as the standard drug therapy, even while raising concerns about the treatment regimen, administration, and physically taking the drug.

“[Our daughter’s] cystine level was sky high at diagnosis and her kidneys were rapidly losing function (stage 3 kidney failure). Her kidney function has stabilized since starting Cystagon… It turned my daughter's quality of life…from miserable to happy and playful;…she finally has strength and energy...”

“My two daughters with cystinosis are both healthy and thriving, because of Cystagon. The medication is affordable even when we had to cover the cost or some of it. Our children's cysteine levels are lower than my husband's and mine (as carriers).” “…Cystagon has definitely slowed the progression. Still at age 16yr my daughter has had a kidney transplant and has developed muscle wasting.”

It is essential to patient health that the cysteine levels are kept at target, but because the drug only lasts in the system for a limited period of time, a large amount of Cystagon must be taken four times a day. Three types of challenges were reported: the large number of capsules and retaining the medication, four times daily dosing, and the very bad taste and odour. Mixed in juice or food or in capsule form, the drug has a bad taste and odour that could cause gagging or vomiting, so it was often difficult to know how much of the medication was actually retained.

Young children often had a gastronomy feeding tube (G-tube) inserted into the stomach to avoid the problems of oral ingestion. Since Cystagon had to be taken every six hours, the other advantage of the G-tube was that children did not have to be awakened for nighttime dosing, which usually took place between midnight and 2 am. However, the G-tube was not risk-free and older children found it undesirable. “He was embarrassed by the bump, never wanted to take off his shirt and couldn’t go swimming with the other kids. We finally had it taken out.”

For many respondents, the biggest impact was the six-hour dosing schedule. “Our lives are lived in

6 hour increments and governed by the strict adherence to a cycle of medication that keeps our child alive. Every aspect of our lives is impacted: sleep patterns, eating schedules, when we can/can't leave the house, how we plan and book holidays…”

“…either my wife or I wake up every night to help my son take his medication… I lose between 1-3 hours of sleep every night. I've notice that this chronic lack of sleep has contributed to reduced cognitive ability at work, increased irritability, reduced sexual drive, reduced desire to exercise and even weight gain...”

The challenges of the bad odour with Cystagon were paramount for some but not others.

“My daughter has been bullied, chastised, and discriminated against her entire life for the unescapable sulphur like skin odour caused by the drug.” One parent of twin 5-year-olds, one with Cystinosis and one without, said, “In daycare, some of the other kids will say something to him; this will probably get worse once he is in school. Even his brother, who is very protective of him, will sometimes say, ‘you stink!’”

Patients with cystinosis also take a large number of additional medications and/or supplements which can complicate compliance. About 64% currently receive nutrient replacements (sodium, potassium citrate, phosphate, vitamin D) with another 32% said they had used these in the past. Similarly, one-third are taking nutritional supplements while one-third took them in the past. About 78% are currently or were in the past taking stomach or heartburn medicine; about 62% currently are or in the past were taking blood pressure medication; and the same percentage are or were taking anti-vomiting medicine. About 53% are currently or were in the past being prescribed growth hormone therapy and 31%, hormone supplements (thyroid medication, insulin). In terms of other treatment, about 46% have been or are currently on dialysis, and more than 60% say they have had or are indicated for a kidney transplant.

Overall, while Cystagon (cysteamine treatment) is recognized as saving the lives of patients with

cystinosis, it does not resolve all of the clinical problems associated with the disease, including deficits in sight, hearing, and cognition. Moreover, it is very difficult to completely adhere to the very strict therapeutic regimen, resulting in serious complications including diabetes, kidney failure and death.

5. Improved Outcomes

Almost all of the respondents were aware of the new drug therapy Procysbi (cysteamine bitartrate), which is the delayed-release formulation of cysteamine, with 86% responding they knew about the differences with Cystagon and only 11% unaware of the drug or how it differed. Canadian knowledge was similar.

Participants’ expectations focused on the potential benefits of a twice-daily dosing schedule and hopes for improved effectiveness and tolerability. Not only would the elimination of a “middle-of-the-night” feeding significantly improve sleep and quality of life, it would also alleviate the issues of the “mid-day” feeding for the school-age child. They hoped that the slow-release formulation would also

increase the likelihood of a continuous level of the drug in the body, keeping cysteine levels low. Many expected (hoped) the drug's slow-release formulation would cause fewer side effects, such as nausea and odour.

"The impact on the family's well being of sleeping through the night would be significant. I've also heard that there is a good chance that the body and breath odour associated … would be reduced. As [my son] enters school, that becomes increasingly important for his social and emotional health. Also, taking away the need for a middle of the day administration at school would also help [him] have a more normal daily routine like the rest of the students." "It would mean my daughter and my husband and I could all sleep through the night. It would also mean that my daughter would not have to take it while at school. My hope is that her nausea will decrease to the point that she rarely vomits which will also in turn increase her appetite." "Because its slow release I think it will maintain a more level degree of the drug in the patients system."

It would be impossible to over-emphasize the experienced burden reported by parents of waking up every single night to administer medication and recognizing that one will never get a full night's sleep for the rest of the life of the child, because the medication is so important.

However, not all patients and parent were prepared to switch, based in part on the lack of long-term experience and data about impact over time. *"We have not switched from Cystagon to Procysbi... After much research, and talking to many specialists, we feel it is in our best interest to stay with what works and has research, years of proof..." "My greatest concern with switching to a new formulation of the drug is that there are no long term studies on the impact of Procysbi on the body over time.… We know that cystine can be measured in the blood, but to what degree the drug is being absorbed into the muscles and organs is not known."*

Finally about one-third of the respondents identified cost as a potential barrier to access. Many are aware of the difference in price; some are concerned about being able to afford their portion of the cost, even with insurance. Most want assurance that Cystagon will still be available to patients who want or need it.

"I am very much hoping that Procysbi will be available to Canadian families at a reasonable cost.

"Cystagon has been covered by Trillium drug benefits, not sure about added cost or continued coverage, which would be a disaster for anyone that has been treated for around 25 years." "The concerns in switching from Cystagon to Procysbi for me is affordability... Since we've not been able to find a health insurance company that will cover Cystagon I don't think they'll be any more likely to cover Procysbi..."

Overall, most patients and parents feel that Procysbi should be available through the public drug plan.

6. Experience with Drug Under Review

About 35% of all respondents have had access to Procysbi, although only 15% of the Canadian-only cohort has Procysbi experience. Among the total group of respondents, 6% say they are receiving the drug through a clinical trial, 24% through an expanded trial or compassionate access, and 59% as a drug plan benefit. Among the Canadian-only cohort, 20% are receiving the drug through a clinical trial and 80% through expanded or compassionate access. No one has yet been covered through a drug plan.

Almost all those on Procysbi were very positive, especially in terms of the twice-daily dosing schedule, positive impact on quality of life, greater tolerability with fewer side effects, and hope for better long-term effectiveness on symptoms and disease progression. Probably most evident is improved compliance.

"… compliance is very important and Procysbi allows more easy with that and not to mention how better tolerated it is, because you take less the symptoms are less. Which makes people more complaint."

"Procysbi has made our lives incredibly better. It has made it much easier to be compliant with the drug, it has allowed us to sleep through the night, and it has given us much more freedom to live our lives." "We have been lucky to be able to have access to Procysbi for 2 years now. My" husband's levels have decreased significantly and taking the medicine twice a day has helped him with taking the medication outside of work hours instead of every 6 hours like Cystagon requires."

Some have experienced immediate benefits in terms of side effects; others have not. And most patients are realistic in acknowledging that the long-term benefits will not necessarily be evident in the short-term.

“Because Cystinosis doesn't manifest "symptoms" with missed dosages, this isn't really an appreciable difference.” “The most important benefit no middle of the night dose. Improvement on quality of life.” “It is much better for our children, and for us a caregivers. Our kids have less stomach upsets.”

When asked specifically about the potential risks and side effects, most of those on Procysbi reported few or no adverse effects. One patient reported that the cysteine levels seemed to be less consistent.

‘Side affects have been minimal but there does seem to be less consistency when levels are tested.” “No side effects experienced other than mild stomach discomfort if not taken correctly.” “There is still a slight odour. Sometimes there is minor GI upset. It is far better than the alternative: to live without the drug would be devastating.” “The side effects with Procysbi are…significantly less. The only downfall with Procysbi is the number of pills required since it only comes in 75mg capsules.”

Overall, patients who have had access to Procysbi feel the benefits far outweigh the potential risks and the “unknown” long-term effectiveness. One patient wrote, “I was diagnosed at age one. I have been on Procysbi for 7 years. This medication changed my life. I no longer feel weak, have stomach upset, feeling dizzy and nauseated, I feel like I can do most that the average person can do because of this drug.... I don't feel like I even have Cystinosis most of the time.” “We have Procysbi and it no comparison to Cystagon. Vomiting stopped, our quality of life greatly improved with 12-hour dosage. Almost no side effects for our daughter.”

“It is crucial that this drug is made affordable for all that have Cystinosis... This is a huge benefit for the Cystinosis community and will help so many.”

Patients and parents in Canada express frustration at the limited clinical trial access to Procysbi. Some of parents who participated in a clinical trial reported that they had to do their own research to find sites that would accept Canadian patients and then travel regularly for testing and monitoring.

7. Anything Else?

Patients and parents expressed a strong preference for Procysbi and felt it should be available through the public drug plan. They were asked to rate “how important” it was to have Procysbi available as a treatment option, regardless of their personal preference. Overall, 94% said it was “very important” and the remainder said it was “important.” However, about one-third raised the issue of cost and affordability and the need to have continued access to Cystagon through SAP, as a choice and also if Procysbi was not available to all. When asked to rate the importance of having Cystagon available as an option, about 92% said it was “very important” and 2% said it was important.

Appendix 1: Patient Group Conflict of Interest Declaration

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

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

   No outside help was provided. CORD performed the background research, conducted the interviews, prepared the survey, analyzed the data, and prepared the submission.

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.

   See above.

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
Horizon			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: Durhane Wong-Rieger

Position: President & CEO

Patient Group: Canadian Organization for Rare Disorders

Date: 31 July 2017