CADTH

CADTH COMMON DRUG REVIEW

Patient Input

NITISINONE (NITISINONE)

(Cycle Pharmaceuticals Ltd.)

Indication: Hereditary tyrosinemia type 1

CADTH received patient input for this review from:
Canadian Liver Foundation

February 9, 2018

Patient Group Canadian Liver Foundation

1. About Your Patient Group

Founded in 1969, the Canadian Liver Foundation (CLF) was the first organization in the world dedicated to supporting education and research into all forms of liver disease. Today, the CLF continues to be the only national health charity committed to reducing the incidence and impact for Canadians of all ages living with or at risk for liver disease. The CLF is the only registered charity in Canada directing funds specifically for liver disease research in all its forms and has invested more than $30 million in the scientific search for causes, preventative measures and potential treatments for liver disease, including hereditary tyrosinemia type 1, a rare form of liver disease. The CLF reaches millions of Canadians through our public and professional education programs, patient support programs and other awareness, fundraising and outreach efforts. Over the past 45+ years, the CLF has invested more than $50 million in health education and prevention programs.

2. Information Gathering

Hereditary tyrosinemia type 1 is a rare disease in Canada, however, in September 2017, we were successful in securing input from 48 people who responded to our call for patient input for the CADTH reviews for two other treatments for hereditary tyrosinemia type 1 (Orfadin and Nitisinone-MDK). The respondents provided very descriptive and informative comments about their experiences.

With this third treatment option up for review by CADTH, the CLF reached out to these same respondents to find out if any of them had any experience with Cycle Pharmaceuticals' NITISINONE Tablets.

Unfortunately, none of the original respondents indicated any personal experience with this new treatment option and we therefore have no additional input regarding direct experience with Cycle Pharmaceuticals' NITISINONE Tablets.

The responses in this submission are based on the input provided by patients, caregivers and health professionals for the previous nitisinone products (Orfadin & Nitisinone-MDK) as their experience with hereditary tyrosinemia type 1 and their expectations for new treatment options remains applicable to this submission.

Demographic information of the respondents to the online questionnaires for the two previous nitisinone treatments (Orfadin and Nitisinone-MDK) was requested in the questionnaire, but response was not mandatory. Below is a summary of the demographic information voluntarily provided by the respondents:

Respondent Categories:

Patient	Caregiver	Health Professional	TOTAL
6	36	4	48

PATIENT Demographics: Age:

Under 18	18 – 24	25 – 34	35 – 44	45 – 54	55 – 64	65 and over
	2					

Sex:

Male	Female	X

CAREGIVER Demographics: Age:

Under 18	18 – 24	25 – 34	35 – 44	45 – 54	55 – 64	65 and over

Sex:

Male	Female	X
	4	

HEALTH PROFESSIONAL Demographics: Age:

Under 18	18 – 24	25 – 34	35 – 44	45 – 54	55 – 64	65 and over
			1			

Sex:

Male	Female	X

3. Disease Experience

Hereditary tyrosinemia is a genetic inborn error of metabolism associated with severe liver disease in infancy. The disease is inherited in an autosomal recessive fashion, which means that in order to have the disease, a child must inherit two defective genes, one from each parent. In families where both parents are carriers of the gene for the disease, there is a one in four risk that a child will have tyrosinemia.

About one person in 100,000 is affected with tyrosinemia globally. However, the disease is particularly common in the region of Saguenay-Lac-St-Jean, Quebec where on person in 20 is a carrier of the defective gene, and one person in 1,846 is affected with the disease.

In the acute form of the disease, abnormalities appear in the first month of life. Babies may show poor weight gain, an enlarged liver and spleen, a distended abdomen, swelling of the legs, and an increased tendency to bleeding, particularly nose bleeds. Jaundice may or may not be prominent. Despite vigorous therapy, death from hepatic failure frequently occurs between three and nine months of age unless a liver transplant is performed.

In the chronic form of the disease, there is a gradual onset and less severe clinical features. In these children, enlargement of the liver and spleen are prominent, the abdomen is distended with fluid, weight gain may be poor, and vomiting and diarrhea occur frequently. Affected patients usually develop cirrhosis and its complications. Without treatment, these children may also require a liver transplant.

Life with tyrosinemia, both as a patient and a caregiver, is extremely demanding physically, mentally and financially. The daily life-saving treatment regimen involves constant vigilance and strict adherence to medication, supplements and a very complicated low protein diet. There is tremendous pressure on the caregiver to ensure strict adherence to this regimen as deviation from any of these components may lead to neurological seizures, kidney and eye problems, liver transplant or death. Parents will go to great lengths to do whatever they can to maintain the demanding medication and diet regimen, but this often means that the lives of the patient, the caregivers and the entire family revolve around medication schedules and dietary restrictions.

"We are parents of 3 kids – 2 with tyrosinemia and 1 without. Our family faces a lot of challenges:

- *Cooking 8 different kinds of meals per day*
- *Not able to work on a regular basis*
- *Watching children 24/7 to make sure that they don't eat restricted food*
- *Regular hospital visits*
- *Lack of a social life – avoiding large family and friends gatherings*
- *Financial hardship*
- *Building kids' personality – training them to accept themselves as being different from other children*
- *Food training – what to eat and what not to eat*
- *School training – ensuring school environment understands and respects the importance of adherence to regimen*
- *Our life is very different than other people. We have to think 10 times before we take any step in life."*

– Parent 1

"Medication is the #1 way to control the disease, then comes controlled diet and ultimately the special milk. This is a constant and daily concern. The challenge is to ensure that my child takes his daily medication as well as a phenylalanine supplement. To provide my son a low protein diet on a daily basis, I must weigh and measure everything he consumes to ensure that we reach the required number of proteins every day without exceeding it. I must prepare the special milk for him every day and make sure that he drinks it in its entirety to ensure his growth." – Parent 2

"In order to provide my child with a low protein diet, I must create daily menus different from those of the rest of the family. I have to reorganize my work schedule according to the time it takes to cook 2 different meals, plus the time for daily preparation of the special milk and the time to make sure my child takes his medication and supplements. It also takes a lot of time for medical appointments (at least 4 times per year) which are essential for the follow-up of the disease." – Parent 3

"The monitoring of tyrosinemia requires extreme rigor to ensure the taking of [nitisinone] NTBC medication and supplements. You need to learn how to do the blood tests to assess the level of tyrosine in the blood every week, then once per month. Every three months a food journal containing nutrient intakes of protein must be presented to the doctor and the data must be converted to ensure that this is the appropriate quantity for the development of our child. Financially, there are many costs including time away from our workplaces, parking fees, industrial weighing machines to measure food quantities, a portable refrigerator and the cost of the low protein diet foods and special milk." – Parent 4

4. Experiences with Currently Available Treatments

When a diagnosis of tyrosinemia is confirmed, physicians should immediately start the patient on nitisinone. It is critical to start medication quickly to prevent further liver and kidney damage and avoid potentially significant complications such as hemorrhage, porphyria-like crises, rash, low blood pressure and severe pain. The patient must also follow a strict diet low in tyrosine and phenylalanine (i.e.: a low- protein diet). Infants/children with severe acute liver failure when diagnosis is made should be assessed for a liver transplant.

Regular monitoring tests are imperative to check the response and to monitor progress. It is recommended that in the first year the patient is evaluated every month until the patient is stable and the family is confident in administering the strict medication and diet regimen. Thereafter, the monitoring interval schedule can be extended.

Before nitisinone was available in the early 1990s, complications of tyrosinemia included cirrhosis, liver failure and liver cancer. Even if the patient is taking nitisinone, long term complications of the disease may still occur, most notably the development of liver cancer. Nitisinone must be taken without interruption.

Patients, caregivers and physicians unanimously and emphatically confirm that nitisinone saves lives and allows patients and families a chance to have a normal life. The dietary restrictions and doctors visits are extremely taxing and costly, but the medication is life-changing.

"Patients generally have no side effects. I have been working with tyrosinemia for over 15 years. It is a revolutionary treatment." – Health Professional 1

"Since there was no medicine and low-protein food was non-existent, I managed to survive until the age of ten with only a low-protein diet, just long enough to get a liver transplant. As I am one of the first people to get transplanted in Quebec, I live with uncertainty in the future." – Liver Transplant Patient

"I started treatment at the age of 5 and before that I experienced the disease with its negative effects with neurological crises and numerous hospitalizations. My life changed completely with the arrival of NTBC in 1993. It has been 22 years since I started taking the NTBC and I have not been hospitalized for the disease since that time." – Pregnant Patient

"It is a child with tyrosinemia, therefore more difficult daily to succeed in making him take his medications, follow his diet or drink his formula of milk. Our lifestyle is completely different from a "normal" family. The medical follow-ups are very difficult. Also we must make sure to receive nitisinone well in time… we are often afraid of missing a dose. We rely on Ste-Justine Hospital to send us the medication on time."
– Parent 1

5. Improved Outcomes

Nitisinone is currently available in Canada under the brand name Nitisinone-MDK and Orfadin, two medications that are also under review by Health Canada; many patients are currently receiving these medications from the hospital through the Health Canada Special Access Program and have experienced the life-saving impact of these treatments. NITISINONE Tablets by Cycle Pharmaceuticals is new to the Canadian market and although it is medically equivalent to the brand Orfadin, it has some differences that might be beneficial to patients and their caregivers. Cycle Pharmaceuticals' NITISINONE tablets only require storage at room temperature, which might allow patients and their families the added freedom to travel and not be restricted by medication that would otherwise require refrigerated storage, (such as Orfadin). NITISINONE tablets can be taken before, after or during food consumption allowing some leeway for the daily medicated dosage. They are also made small in size and would be easier to swallow especially for children or patients who have difficulty taking pill form medication. These variances compared to the other nitisinone products allow patients and caregivers more flexibility with living with tyrosinemia, a disease that requires a restricted diet and a lifelong medicated lifestyle starting from early childhood.

6. Experience with Drug Under Review

The patient/caregiver experience with other brands of nitisinone has been well-established as this treatment has been available since the early 1990s and the patients and caregivers who responded to our questionnaire received their medication through the Health Canada Special Access Programme and secured their medication through the hospital pharmacy.

The patient often responds to nitisinone quickly, with blood clotting issues resolved and improved liver function within one week. The demand for this drug remains extremely high as the life-saving impact on the patient is immeasurable. NITISINONE Tablets by Cycle Pharmaceuticals have not been available in Canada and we did not receive any input from patients who had used this brand of nitisinone.

"My son is alive. This is the main effect of nitisinone. My son did not need a liver transplant. He takes his nitisinone and he can live. We are not talking about a small drug to control mood or dry skin… we are talking about avoiding neurological crises and children who died before 3 years. Side effects, there are none."
– Parent 1

"The use of nitisinone has controlled the amount of tyrosine and phenylalanine since the birth of our son. Since the diagnosis, his disease is very well-controlled and the medication is the main reason. Nitisinone allows our son to live simply." – Parent 2

"Positive effect of nitisinone = almost no more liver transplants." – Health Provider 1

"Nitisinone helps the liver to remain optimal and functional." – Health Provider 2

7. Anything Else?

Without question, treatment for hereditary tyrosinemia, regardless of brand, must be universally accessible and affordable to patients in Canada. Any systemic disruption in medication availability will lead to dire consequences for infants, children and adults with tyrosinemia.

The hope is that access to nitisinone through the Public Drug Program will mean that patients and caregivers will no longer have to travel long distances to access the medication as they would be able to pick it up at their local pharmacy. Furthermore, the hope is that the current no-cost access to nitisinone treatments (regardless of brand) remains in place as there is already a significant financial burden on families due to the strict demands of a low-protein diet.

If accessing nitisinone is not seamlessly and readily available through local pharmacies as part of the Public Drug Program, then there is tremendous fear and anxiety as to what impact this will have on the life of the patient with tyrosinemia.

This sentiment is well-summarized by a tyrosinemia patient who has received a liver transplant:

"Nitisinone is a revolutionary drug that has helped hundreds of Quebec children live with tyrosinemia and have a good quality of life despite the disease. The arrival of nitisinone has completely changed the face of the disease, allowing parents to have hope for the future of their children. The generation that lived before nitisinone experienced a lot of stress, anxiety and uncertainty about the disease. Several children have died. Some of them, like me, were given a transplant, but others did not survive. Tyrosinemia before nitisinone was a terrible disease… this drug must remain accessible to families at zero or low cost since these families will have to bear the cost for many years."

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 assistance was utilized to complete this submission. This submission was completed by CLF staff and volunteers. The only outside input for this submission came from the patients, caregivers and health care professionals who responded to the CLF's online questionnaire.

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.**

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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.**

The Canadian Liver Foundation (CLF) is committed to bringing liver research to life for all Canadians through liver research, education, patient support and advocacy. The CLF receives funding from a variety of sources with the majority coming from donations from individuals across the country. We use these funds to support CLF liver awareness, education, patient support and research grant programs.

The CLF receives some program funding in the form of unrestricted educational grants from pharmaceutical companies. Grant agreements are established in support of activities initiated by the CLF and prohibit the funder from having any input or influence in program objectives or deliverables.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No companies who have direct or indirect interest in the drug under review have provided the CLF with any level of financial payment over the past two years.				

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 Karen Seto

Position: Director, Professional Partnerships & Programs Patient

Group: Canadian Liver Foundation

Date: February 5, 2018