CADTH

CADTH COMMON DRUG REVIEW

Patient Input

NITISINONE (MDK-NITISINONE)

(MendeliKABS Inc)

Indication: For the treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

CADTH received patient input for this review from:

Canadian Liver Foundation

Canadian Organization for Rare Disorders

October 23, 2017

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 $29 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

To gather input for our submission, the CLF invited patients, caregivers and health care professionals from across Canada to fill out an online questionnaire modelled on the CADTH, CDR and pCODR Programs submission template. The online questionnaire was open from August 4 to September 19, 2017 and promoted on the CLF website, via CLF social media channels and to CLF patient, caregiver and health care professional contacts.

Hereditary tyrosinemia type 1 is a rare disease in Canada and as such, the number of responses to this survey were expectedly low, however, the responses received were very descriptive and informative. As the incidence of this disease is higher in the Saguenay-Lac-St-Jean region of Quebec, the CLF's online questionnaire was created and communicated in both English and French.

The responses received have been used to compile the feedback for this submission. Quotes from CLF questionnaire respondents are included in *italics* in various sections of this submission.

Demographic information of the respondents 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			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 through the Health Canada Special Access Programme so many patients are currently receiving this medication from the hospital and have experienced the life-saving impact of this treatment. Patients, caregivers and health providers all agree emphatically that access to this treatment for tyrosinemia is a matter of life or death and under no circumstances can treatment be interrupted or stopped whether it remains available through the Special Access Programme or whether it is transitioned to the Canadian Public Drug Plan. Treatment must be available, accessible and at zero or minimal cost or children will die.

"It should not matter how the drug is accessible to patients as it extremely important to continue taking it since it has been proven over the years. On the other hand, not everyone has the financial means and it is important that the NTBC continues to be easy to access so that all the patients can take it." – Pregnant Patient

"Many patients and families are afraid of financial repercussions. Tyrosinemia already results in several additional costs for families (follow-up outside their region, additional costs associated with low-protein food, costs for certain supplements and other medicines). There are already many costs for families and access to nitisinone through a different system should not cost any more money." – Liver Transplant Patient

"It would be less stressful. Rather than waiting to receive the drug and running the risk of missing it, I could simply go to my pharmacy to look for it. Less stressful also because we are always afraid that overnight this "special" access is removed and that we would lose access to the drug." – Parent 1

"As a parent, we are concerned about the long-term accessibility of this drug to our son's well-being, development and active learning. Our health care system values equal care and I believe it is our honour to continue on this path without any financial discrimination." – Parent 2

"We want access to the drug in the same way as it is now, through Health Canada's Special Access Program, sent by the Ste-Justine pharmacy every 3 months. Why change a winning formula? Why bring families into additional stress in the face of this?" – Parent 3

"Patients would be self-sufficient in their supply, but my concern is about whether they would have to pay. Would all pharmacies be willing to offer it? Could it interfere with adherence? – Health Provider 1

6. Experience with Drug Under Review

The patient/caregiver experience with 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.

"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

"We have used both brands of nitisinone (Orfadin and MDK-Nitisinone) and did not encounter any side effects with both kids." – Parent 3

"Orfadin has been used since the beginning of the life of our boy who is now 12 years old. Recently, he started taking MDK-Nitisinone and we have not seen any changes in that regard. – Parent 4

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

"Nitisinone helps the liver to remain optimal and functional. Both products (Orfadin and MDK-Nitisinone) are easy to administer and saves the lives of patients." – Health Provider 2

7. Anything Else?

Without question, treatment for hereditary tyrosinemia, regardless of brand, must remain universally accessible and affordable to patients in Canada. Any access change must be weighed extremely carefully as 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 the treatment remains in place as there is already a significant financial burden on families due to the strict demands of a low-protein diet.

However, 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.

   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.

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.

   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.

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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.

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 Education & Partnerships
Patient Group: Canadian Liver Foundation
Date: September 19, 2017

Patient Group | Canadian Organization for Rare Disorders

1. About Your Patient 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: interviews with metabolic clinic staff, individual semi-structured interviews, and a survey created and administered by CORD.

The purpose of the clinical staff and individual parent interviews was to gain a rich, in-depth understanding of the experience of patients and families living with Tyrosinenia Type 1 (TYR-1) and their perceptions of their current therapies, including the therapy under review, Orfadin. This background knowledge was used to develop the survey that incorporated the most important aspects of the disease impact and the treatments. The patient interviews, in particular, provided information that served as a framework for interpreting and validating responses to the survey

The individuals interviewed were recruited through two sources, the metabolic clinic (at Toronto Hospital for Sick Children) and the Facebook for the (US-based) Network for Tyrosinemia Advocates Support Group NOTA. The survey was distributed through the same sources, namely the Metabolic Clinic (by individual invitation of the Nurse Coordinator) and notification in the Facebook (courtesy of the group administrator). The Survey was available on Survey Monkey from 8 – 27 September. The survey was available only in English and recruitment also done in English, even though it was recognized that the majority of the patient community lived in Quebec. However, given that the patient access situation in Quebec was somewhat different than in Ontario and the rest of Canada. Moreover, while this input is submitted for the review of Orfadin, all forms of nitisinone were included in the interviews and written survey.

The interviews were conducted with two clinic staff (nurses) and three parents of children with TYR-1 living in Canada. The patients were also encouraged to complete the survey. There were 12 responses to the survey, 11 from parents and one directly from a patient. Of the 12 patients represented, eight were Canadian (six from Ontario, one in Alberta, and one in Quebec). There were two responses from the USA and two from elsewhere (namely the United Kingdom and Israel).

All patients represented were diagnosed with TYR-1, with the breakdown as follows: 75% diagnosed as acute TYR-1 and 25% as chronic or unknown TYR-1. Of these, two (2) were under 3 years old; six (6) were ages 4-7 years; two (2) were between 8 and 18 years old; one (1) was 19 years old, and one (1) was 32 years old. Among the patients, seven (60%) were male and five (40%) were female.

3. Disease Experience

The described patient experiences could perhaps be placed into three categories: those diagnosed prior to available of medication treatment, specifically nitisinone or NTBC (1 patient); those diagnosed without benefit of newborn screening, a.k.a. NBS (3 patients); and those receiving a diagnosis as a result of NBS (8 patients). Overall, prior to available medication, TYR-1 was almost always a fatal condition with children rarely living beyond the age of 10. With the discovery that nitisinone could be used to block the breakdown of tyrosine before it became converted into a harmful product, the condition was no long life- ending but it was still life-altering, requiring strict adherence to medications, medical foods, and diet restrictions. Given all of these challenges, parents and patients appeared to be mostly positive, optimistic, and accepting of the condition. They were aware that a viable treatment had been available for only a few years and that prior to this, there was little hope of a future for these children. Moreover, other than the strict diet adherence, most of the children functioned normally with minimal or no cognitive impairment or other physical complications if continuously treated. While they were optimistic about a "normal" lifestyle and lifespan (similar to children with phenylketonuria or

PKU), they were also aware that there was no true understanding of long-term prospects of living with TYR-1, since most patients previously had not survived to adulthood, unless they had received a liver transplant.

The experience of symptoms as described by respondents varied according to the age of the patient, which also coincides with delay in diagnosis and access to treatment at time of diagnosis. Prior to 2002, there was no readily available treatment in Canada to manage TYR-1 and prior to 2007, there was no newborn screening in Ontario (where majority of these respondents reside). Only one respondent (diagnosed prior to available medication) reported liver failure and subsequent liver transplant. *"When our daughter was diagnosed in 1985, we did not have the option of using nitisinone. When she was initially diagnosed … we had to research the disorder and then working together with the doctors and governments in both Canada and the US … [we were able to get her] a liver transplant on her first birthday and [she] is now 32, married and a mommy of two."*

About one-third of parents who responded had children not diagnosed through newborn screening (including one from the UK where newborn screening for TYR-1 is not mandatory). Parents reported that their child had experienced some of the following common symptoms of (untreated) TYR-1 in the past (but not currently): failure to grow (thrive), fever, diarrhea or other gastro-intestinal problems, and/or neurological crises (pain in nerves or spinal cord). These symptoms ceased when the children were diagnosed and put on medication. For two-thirds of respondents, the children (diagnosed near time of birth) had never experienced these crises. However, one-third of all respondents reported their child was currently experiencing cognitive (developmental) delays.

Most of the parents who experienced delayed diagnosis said they were actually relieved to get a diagnosis. *"She was our third child so when she kept losing weight … even though she was breast- feeding well, we knew something was wrong. The doctors … said we shouldn't worry; she would stabilize. But she didn't, so when they called to say she had tyrosinemia, we were initially relieved just to have a name."*

One parent, who had lost a previous infant, said, *"I knew almost right away he had the same condition and we just wanted a diagnosis so we could start figuring out what to do. We were heartbroken to learn that he could have been diagnosed right a birth."*

For all parents, the initial diagnosis (whenever received) was a shock followed quickly by realization of the challenges of managing the condition. This is a lifetime regimen that is comprised of oral medication (nitisinone), nutritional supplements, and a diet with severe protein limitations. Fortunately, in Canada, nitisinone (which is very costly) is funded, primarily through public drug plans with little or no co-pays, but this was not always the case nor currently true everywhere.

"My brother was diagnosed with Tyrosinemia Type 1 when he was 3 months old, so when I was born two years later and started showing the same symptoms, my parents knew right away with me. My mom had fought for months to get my brother on medication and she had to do the same for me, though it was much easier."

"My son was diagnosed only after one week he was born thru post-natal screening. It was very hard to be told and therefore acknowledge my son had a very serious disease and he would spend his life on a medication."

Parents with older children talked about their concerns when the child is at school or away from home.

"The hardest part is when they go to school; how do you keep a 6-year-old from sharing her lunch, swapping lunch, and most of all eating other kids' lunch when everyone else is doing it? We read on Facebook about parents with teens who just don't want to take the drinks or stay on the low protein diet so we are worried about what is to come and how WE are going to deal with it."

"How do you make sure they feel like "normal" kids when they are anything but? We try not to make it about what we want and focus on he wants."

Overall, patients and parents reported overall challenges to adapting their lifestyle to living with TYR-1. According to one parent, *"Tyrosinemia's food management can sometimes be very hard especially when travelling. Your life is greatly affected because institutions are barely ready to deal with kids with special needs."*

Most, however, seem to have made the necessary adjustments, especially when there is support for access medications and supplements. *"Tyrosinemia has affected my life in every which way … I wasn't willing to accept and didn't want to hear. But once you get a hang of it. It becomes way more easier and the fact to know the expensive drugs and food are covered half the tension is gone."*

When asked to rate the impact of living with TYR-1 on school or work life, about one-third reported that the person with TYR=1 was experiencing "some" impact on his/her school or work life; none rated the impact as "severe" or "much." Similarly, about one third of

parents rated “some” impact on their home, family or social life or work life, but none said there was “much” impact and two-thirds reported little or no impact.

Many of the parents talked about the importance of the metabolic clinic or program in helping to learn how to handle the medication and the food management.

“Because the condition is so rare, we don’t know any other families with the disease. The clinic here is wonderful and I don’t think we could have survived the first six months without them. They took the time to go over everything, how to prepare the medication (that comes in capsules), what to do if they get sick and throw it all up?” Truly, TRY-1 appears to be a well-tolerated condition so long as medication and special diet foods were accessible.

4. Experiences with Currently Available Treatments

This question is a bit challenging to answer since all of the patients are currently using the medication under review (Orfadin capsules) or had used it in the past. Those who had been switched were prescribed a bioequivalent version of the same medication (MDK-Nitisinone), available in the same capsule format. Two patients (in the USA) reported using Orfadin oral suspension, but no respondent had used Nityr (nitisinone tablets), even though it had been approved in Canada. All patients (with the exception of the one who had a liver transplant) were also taking medical food supplements and following a low-protein (protein-restricted) diet. One patient had used a blood-clotting replacement factor in the past.

All respondents said they had not experienced any serious or frequent negative side effects to any of the treatments, including nitisinone (in any form) or the nutritional supplements. When asked to rate the seriousness of any experienced adverse effects, about half who were currently or previously using Orfadin capsules said they had experienced “not serious or seldom” effects that included “stomach bloating or pain, feeling tired or weak, loss of appetite or weight.” About the same number reported similar responses to Orfadin oral suspension.

About half of the patients using MDK-Nitisinone capsules reported “not serious or seldom” effects, as noted with the other medications, However, this difference (in percentage) does not seem to reflect any true difference in adverse effects of the medications.

The most frequently reported challenge was administration to infants. *“It was hard when he was a baby to mix and syringe into his mouth after opening capsules.”*

“In the beginning, he would gag or refuse the medicine, so we had to mix with food. But he still didn’t seem to like the taste.”

“Now that she’s older, it’s a lot of pills but she takes them all without complaining. The drinks and diet are much harder. We’ve had to get very creative to make meals that make her feel like she’s eating the same as her brother.”

When patients who had been switched from Orfadin to MDK were asked about any experienced differences, most said they were initially concerned because it came in different packing and the medicine looked different. They had not been advised at the clinic that the drug was being switched, although they were informed at the pharmacy that it was the same medication.

“It would have been good if we had been told ahead of time. We called the clinic and they said they had no idea the medication had changed. We were pretty much on edge and felt we had to be on watch all the time.”

“I asked if our original drug was still available and the pharmacy said this was the only one that was approved (paid for), so we didn’t have a choice.”

“It seemed like we had just gotten her to accept the medicine without fuss so I wasn’t pleased to switch. I’m not fully convinced they are exactly the same but we haven’t had any problems.”

Overall, as noted in the previous section, parents (and patients) were very grateful to have a medication that most described as “life-saving.”

“When we talk to some of the other parents on Facebook, I feel very lucky that we received the diagnosis at a time when there was a medication available. And the medication is completely covered by the clinic.”

"We got the diagnosis about 10 days after our baby was born, and the doctor started us on Orfadin right away. It was a miracle because he was so much more lively and started to put on weight."

5. Improved Outcomes

This is also a challenging question to answer in the current context. While all patients would like to have a cure for TYR-1, most provided more realistic wishes. In interviews and written comments, respondents raised all of the following desires for improvements in treatment:

- Liquid formula for infants (actually available as Orfadin oral suspension)
- Less frequent dosing (once a day) (actually available with Orfadin in USA)
- Easier to take pills (approved in Canada as nitisinone tablets)
- Medication that is easier to travel with (approved for more days with refrigeration in the USA).
- Better tasting medical foods
- Transdermal patch (perhaps not realistic)
- Anything that would allow a more "normal" diet

These patients and parents appear to be more challenged by the diet restrictions than the medication and even the nutritional supplements (medical foods). They would like a medication that would allow their children to eat more "normal" diets or at least to decrease the protein restrictions but, overall, they find the treatment regimen manageable. However, most worry about how well their children will adhere to all of this as they grow older, having witnessed through Facebook and other support groups the frustrations expressed by parents of older children and the young adults themselves.

6. Experience with Drug Under Review

The access to the medication under review was addressed in the previous sections. Most families in Ontario have been switched from Orfadin to MDK-Nitisinone when the latter received market authorization and a DIN. Previously, Orfadin had been available only through SAP. The parents were not really aware of the SAP process since this was done by the clinicians, and most had experienced some frustration and concern when MDK was substituted for their usual Orfadin medication. However, most did not report any difficulties in the transition

When prompted (in the interviews and also in the surveys), all reported they were "satisfied" with Orfadin nitisinone capsules as well as MDK-Nitisinone capsules; none were dissatisfied. Among those using Orfadin oral suspension, all were also satisfied. One parent in he USA reported the patient was taking Orfadin once daily (instead of twice), as recently approved by the US FDA, and was also satisfied with this change.

When prompted further, 80% (8 of 10 responding to question) rated the availability of "more than one form of nitisinone for patients with TYR-1" as "very important" and the remaining 20% said it was "important." When asked for clarification, most cited concerns about potential manufacturing disruptions (especially with a small and new supplier) as well as potential supply shortages. Most said they would be concerned if there were other equivalent nitisinone capsules introduced and they were switched on the basis of price alone. Most indicated they would prefer to have Canada introduced improved products rather than duplicates of existing products.

7. Anything Else?

Parents and patients affected by TYR-1 are very grateful to have a medication that effectively reverses the condition from life threatening to manageable. They are aware that there is evidence as to the drug's effectiveness over the very long-term but they are optimistically, given its 15 to 20-year history. When asked, they are very concerned that companies are motivated to continue to invest in finding improvements in therapy, even though this is a very small patient population. They are hopeful that companies will want to research the applicability of medicines for related metabolic conditions (like PKU) and to do more clinical trials with the TYR-1 population. They would also like to ensure there is on-going investigation of the implications of treatment into adulthood as well as have continued research on issues related to TYR-1 and aging. This will require funding by governments but especially by companies that have a commitment to TYR-1. It would be important that Canadians are included in those studies.

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, this was completed by CORD without additional outset help.

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, information was collected, analyzed, and prepared for submission by CORD.

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
Sobi	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: 1 October 2017