

CADTH Reimbursement Review

Patient Input

TRIENTINE HYDROCHLORIDE (Waymade-Trientine)
(Waymade PLC)

Indication: Wilson's Disease

CADTH received patient input from:

Canadian Liver Foundation

July 23, 2021

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CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

CADTH Reimbursement Review Patient Input Template

Name of the Drug and Indication	Trientine Hydrochloride (Waymade-Trientine)
Name of the Patient Group	Canadian Liver Foundation
Author of the Submission	[REDACTED]
Name of the Primary Contact for This Submission	[REDACTED]
Email	[REDACTED]
Telephone Number	[REDACTED]

1. About Your Patient Group

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 nearly \$38 million in the scientific search for causes, preventative measures and potential treatments for 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.

2. Information Gathering

The CLF invited patients, caregivers and health care professionals from across Canada to fill out an online survey modelled on the CADTH submission template. The online questionnaire was promoted via CLF communication channels. A total of 8 respondents provided input for this submission: 5 patients and 3 caregivers. A total of three patients were from Ontario and two from Manitoba. Two caregivers were from Nova Scotia and one from Ontario.

The responses received have been used to compile the feedback for this submission. Patient and caregiver input from a previous trientine hydrochloride input submission was also used in this reimbursement review submission. Demographic information of the CLF online survey respondents was requested in the survey, but response was not mandatory. Quotes from CLF questionnaire respondents are included in *italics* in various sections of this submission. Also included in this submission is input from two health care professionals (HCPs). Their input was not in direct response to this call for patient input but still provides very valuable insight to be considered during the review process.

3. Disease Experience

Wilson disease is a hereditary disease in which excessive amounts of copper accumulate in the body, mainly in the liver. The disease affects approximately one in every 30,000 Canadians. Small amounts of copper are essential to good health. One of the liver's jobs is to maintain the balance of copper in the body. The liver is also the main organ to store copper. In Wilson disease, when its storage capacity is full, copper is released into the bloodstream. It then accumulates in various organs such as the brain and the cornea of the eye. This copper overload damages these organs. Left untreated, Wilson disease can be fatal.

In the 1950's and 1960's, D-penicillamine and trientine were developed as oral treatments for Wilson disease. Medical treatment is highly effective in Wilson disease patients, permitting good health and a normal life span in most. However, D-penicillamine causes major adverse effects in 30%–40% of Wilson disease patients. Trientine, an alternative treatment that removes and enhances the removal of copper by the kidneys, is suitable in patients who do not respond well to D-penicillamine, and is as efficacious as D-penicillamine with significantly fewer side effects. Most importantly, trientine is recognized as a lifesaving medication for the subset of Wilson disease patients who require chelation therapy (a chemical process in which a synthetic solution is injected into the bloodstream to remove heavy metals and/or minerals from the body) but cannot tolerate long-term D-penicillamine. Trientine is approved by Health Canada and now manufactured in Canada which improves availability, however barriers relating to access and reimbursement in various provinces have been identified.

Wilson disease patients indicated that their ability to exercise, work, travel, conduct household chores, ability to spend time with family and friends, and to fulfill family obligations have been the most impacted day-to-day activities. Caregivers have indicated that their ability to work and travel has been impacted.

“Wilson Disease has impacted every aspect of my life. From the constant doctor's appointments to my numerous health problems, WD changed everything for me.” – Patient

“I was diagnosed when I was 14 years old, I am now 28 years old. I have suffered from liver cirrhosis, neurological issues, mental health problems, and a wide range of gastrointestinal problems.” – Patient

“The time, effort and severe stress constantly trying to acquire trientine for my daughter. Besides Wilson Disease she has other medical conditions which impact her health greatly.” – Caregiver

“Pre-chelation, I was in University and my studies were impacted - developed a tremor in my hands so writing was difficult, and I withdrew socially.” – Patient

“I have been pulled from working since September 2019. It has caused me to have stage 4 liver cirrhosis and some neurological symptoms. My life has been drastically altered since my diagnosis.” – Patient

“Before diagnosis, definitely impacted. Major depression, blood clotting impaired, skin rashes, etc. The depression I made it through, but that was very hard on everyone around me, and it almost cost me a job.” – Patient

4. Experiences With Currently Available Treatments

Zinc acetate is a salt of zinc used to inhibit the absorption of copper in patients with Wilson disease, and is indicated for maintenance treatment of patients who have been initially treated with a chelating agent. There are very minimal side effects to zinc acetate, the most common being an upset stomach and elevated liver and pancreatic enzymes.

D-penicillamine is a common treatment for patients with Wilson disease. D-penicillamine is a chelating agent that helps remove copper from the body. Common side effects include stomach/abdominal pain, nausea, loss of appetite, diarrhea, itching or rash, poor wound healing, increased wrinkling of the skin and worsening of neurological symptoms. D-penicillamine can be used during pregnancy in Wilson disease patients even though it is not generally recommended for use during pregnancy in people who do not have Wilson disease.

Trientine is a chelating agent that works by removing heavy metals from the blood used to treat Wilson disease in people who cannot take D-penicillamine. Trientine works much like D-penicillamine but tends to cause fewer side effects. Still, neurological symptoms can worsen when taking trientine. Common side effects of trientine include skin rash, muscle spasm or contractions, heartburn, stomach pain, loss of appetite, or skin flaking, cracking, or thickening. The recommended initial dose of trientine is 500-750 mg/day for pediatric patients and 750-1250 mg/day for adults given in divided doses two, three or four times daily. This may be increased to a maximum of 2000 mg/day for adults or 1500 mg/day for pediatric patients age 12 or under.

Those living with Wilson disease have indicated emotional and psychological effects while managing their illness with currently available treatments. Constant stress, fear and psychiatric symptoms (which could be the effects of brain tissue damage caused by copper accumulation or perhaps the consequence of a co-morbidity with emotional disorders) have been identified, along with cases of bipolar disorder. Psychiatric symptoms further complicate the course of any disorder, since anxiety and depression have a negative impact on quality of life and undermine the compliance needed to achieve disease regression. The lack of emotional and behavioral control can further impact the social life of patients, worsening the impairment and the disability caused by Wilson disease symptoms.

When gathering input from patient and caregivers, intolerable side-effects to current treatments (ranging from complete to somewhat) included: fatigue, lack of appetite, nausea and pain. Tolerable side-effects (ranging from somewhat to very) included: fever, dizziness, forgetfulness and stomach irritation. Other side effects that patients and caregivers mentioned with past treatments included feelings of lethargy, abnormal skin tightness, tingling hands and/or peripheral neuropathy, decreased platelet count, constant muscle tension and splenomegaly.

“I have been on Trientine since I was diagnosed when I was 14. There are some definite issues with side effects, on your stomach but it is better to be poisoned by copper. Zinc made me feel nauseous the first time I took it. But now I take it daily. Basically, the medication makes me feel sick, but I do not want to die from copper poisoning.” – Patient

“Constant chronic pain from muscle tension has decreased my quality of life.” – Patient

“Shelf life of her medication is only 10 days and we have to order in advance as it has to be made especially for us and it takes a few business days to get the order in. We risk running out before the new order comes in and we can't go anywhere for long periods of time as we can't bring extra refills with us.” – Caregiver

5. Improved Outcomes

Trientine is a chelating agent that works by removing heavy metals from the blood used to treat Wilson disease in people who cannot take D-penicillamine. Trientine works much like d-penicillamine but tends to cause fewer side effects. Trientine is approved in Canada, however barriers relating to access, cost and reimbursement in various provinces have been identified by patients, caregivers and health care professionals.

When asked how important it is for patients to have access to Wilson disease treatments, both patients and caregivers indicated that it is “very important”. The patients also indicated that it is “very important” for them and their health care professional to be able to make a choice of treatment(s) based upon each different treatment’s known side effects. Patients indicated that it was “more so important” and/or “very important” when considering taking additional Wilson disease treatment in reducing short term and/or long-term side-effects, overall improvements to quality of life and chance for long-term stability.

Patients, caregivers and health care professionals have highlighted barriers and limitations in accessing treatments for their Wilson disease. This included various financial challenges, issues with the Special Access Program for trientine, lack of government support (through various provincial organizations) to cover costs for medications, issues with obtaining support from various insurance companies, as well as reimbursement requests being denied.

“The time, effort and severe stress constantly trying to acquire trientine for my daughter. Besides Wilson Disease she has other medical conditions which impact her health greatly. It is vitally necessary for her to have access to trientine at a reasonable price or her health will be seriously compromised. The games drug companies have played with this drug and put undue stress on my daughter and family. This is mainly due to severe price increases and availability.” – Caregiver

“Difficulty with accessing medication upon diagnosis, and cost of medications.” – Patient

“Insurance companies are refusing to provide insurance for life and mortgage without a crazy amount of medical data. Even with that, they can reject my applications.” – Patient

“My issue is how medication support is decided between govt and insurance companies. It really doesn’t live up to the ideal of health care coverage.” – Patient

Patients and caregivers indicated and health care professionals have highlighted barriers and limitations in accessing treatments for their Wilson disease. This included various financial challenges, issues with the Special Access Program for trientine, lack of government support (through various provincial organizations) to cover costs for medications, issues with obtaining support from various insurance companies, as well as reimbursement requests being denied.

When asked what improvements they would like to see in a new treatment that is not achieved in the currently available treatments, how might daily life and quality of life be different if new treatment provided those desired improvements, or what trade-offs would they consider when choosing therapy; patients and caregivers indicated that having access to medication along with insurance coverage is the most crucial aspect as most people living with Wilson disease still do not have access to trientine. Another important point mentioned was more clinical trials in Canada for Wilson disease treatment as an effective method to increase treatment options for those living with this disease.

“Not having access to life-saving medication is a terrible feeling. Not having access to my medication makes it feel like the government has failed me and they are willing to let me and others with WD die.” – Patient

“It is very difficult to access Trientine in my region. The medication is very expensive approx. \$2000 a prescription, of which I cannot afford to pay. Trientine recently got a DIN in Canada. Originally, I was under the impression it would be more accessible but the fighting with insurance and the province to see who is going to cover what and if they are going to cover anything at all has made it very difficult. I still have to pay ~\$250 per bottle.” – Patient

“A once a day pill would improve drug compliance in adolescents. Ultimately we are hoping for a cure, perhaps stem cell treatment. Cost has always been a huge concern. The ability of adult children to become independent of their parents financially as they try to manage health care costs Complications due to comorbidities. We can't determine what is causing the symptoms, disease, medications, mental health or other chronic health conditions. Our daughter is 28 and still needs her parents help to lobby government, drug companies, insurers. There is the constant stress of not knowing if she will have continued access to her medication.” – Caregiver

“Having to take less medication or not as often.” – Patient

“Different, readily available treatment options for people with Wilson disease available in Canada. Without all of the red tape that is currently experienced. It's a lifesaving medication and we should not have to jump through hoops in order to receive it in Canada.” – Patient

“New medications are being trialed outside Canada. Seems to be a wall when it comes to Canada. I'd like to know why and see if that can be changed. Those meds sound much better to my long-term treatment and effectiveness.” – Patient

“I would like to see treatment options be more available in Canada, along with clinical trials. And affordability and coverage with existing govt health coverage is ideal and desired.” – Patient

6. Experience With Drug Under Review

Trientine hydrochloride (brand name: Waymade-Trientine) is indicated for the treatment of patients with Wilson disease who are intolerant to D-penicillamine. Trientine hydrochloride (Waymade-Trientine) is a chelating compound for removal of excess copper from the body and is available as 250 mg capsules for oral administration.

Dosages evaluation and/or interval between dose has not been done. However, on limited clinical experience, the recommended initial dose of Trientine Hydrochloride (Waymade-Trientine) is 500-750 mg/day for pediatric patients and 750 - 1,250 mg/day for adults given in divided doses two, three or four times daily. This may be increased to a maximum of 2,000 mg/day for adults or 1,500 mg/day for pediatric patients age 12 or under. Trientine hydrochloride (Waymade-Trientine) works by attaching to the copper, and then passing it from the body. It may also work by attaching to the copper in the stomach and stopping it from being absorbed.

No survey respondents indicated having experience with the drug under review. **The patients and caregivers who have had experience with other currently available trientine hydrochloride products have indicated an array of challenges leading up to gaining access. Respondents pointed out the following challenges:**

- **insurance company support presented with many obstacles**
- **pharmacy channel gaps**

- **issues with ongoing prescriptions**
- **medication contraindications**

“Medication support when changing companies / medical plans. This survey is definitely related to the struggles I've had for getting trientine supported by Manulife for my group plan. They've been very difficult to work with, with no regards to my immediacy for an answer and actual implementation of support.” – Patient

“Had to apply to special access program and waited 3 months to hear back that it had been approved. Then waited for trillium to approve financial compensation and EAP program application and was denied so have to pay out of pocket.” – Patient

“My hepatologist originally applied for the special access program to Trientine but I was denied. My hepatologist has since told me that my only treatment option is solely penicillamine so there is nothing that can be done about my side effects because I am required to be on this medication for life in order to live.” – Patient

“So far, treatment is going well. I am fortunate that our insurance has always paid for the medication. However, many people aren't so fortunate. It is terrible that some folks have financial hardship and they have to forgo treatment altogether. The price of trientine is ridiculous, and I don't want this being a barrier for my child once they come of age. No one should have to decide between paying their rent/groceries and taking a lifesaving medication.” – Caregiver

“I think it is very beneficial to have the option of trientine for those with Wilson disease. When I was diagnosed one year ago my one straightforward option was to start on penicillamine which has many serious and potentially life altering side effects. As I was working in health care during the pandemic, I did not see the possibility of going on that medication due to the potential harms and the potential for not being able to work. Therefore I had to wait 3 months + to be approved to even purchase trientine on my own, which was a huge barrier to access. I hope that this changes in the future as the side effect profile for trientine is much more tolerable and safe than that of penicillamine and therefore should be considered as a fundable and accessible medication in Canada.” – Patient

7. Companion Diagnostic Test

Not applicable – this drug does not require a companion diagnostic test.

8. Anything Else?

The Canadian Liver Foundation believes that liver disease patients, their caregivers and health care providers should have access to the most effective treatment options regardless of geographical location, financial status, treatment status or disease severity in order to ensure the best possible outcomes.

The aim of treatment is to maximize the effectiveness and minimize the adverse side effects with the hope for improved patient outcomes. It is important to ensure greater and more equitable access to important treatments for Wilson disease patients while expanding therapeutic options for patients and healthcare professionals. We think it is crucial that patients across the country have equitable access to all treatments for liver disease and that provincial borders should not be a barrier.

The hope is that access to Waymade’s Trientine Hydrochloride will mean that patients and caregivers will have improved and increased access to trientine as a treatment for Wilson disease. Furthermore, the hope is that the cost of treatment does not increase as this would place a significant and unexpected financial burden on families. However, if accessing trientine hydrochloride (Waymade-Trientine) is not seamlessly and readily available as part of various provincial reimbursement programs, then patients will have less access to these life-saving drugs.

“There are not many options for families other than to beg for government help. It is very challenging when we are talking about orphaned drugs for a rare disease. Each patient and family is fighting an exhausting and often very lonely battle.” – Caregiver

“Patients trying to get approval from insurance are running into obstacles with no clear paths. There are a few things to be addressed related to acceptance and implementation of the medication now that it is approved for Canada.” – Patient

“We finally have options. I would hope the doors don’t get closed down by insurance companies. That’s almost worse than having to go through the SAP.” – Patient

“If it’s available for Canadians, I would love private insurance companies to cover it as well vs provincial drug plans because the province has a deductible that is about \$11,000 in my case and that’s a cost that I would never be able to afford.” – Patient

“I do not understand why life-saving medication is so inaccessible. I didn’t ask to be this way so why am I being punished?” – Patient

“This medication needs to be more accessible to all.” – Caregiver

“Please consider having this a readily available medication in a first line treatment for those diagnosed with Wilson Disease. Also, please have the same treatment options available throughout all of Canada and not different in other provinces. We are all the same, it shouldn’t matter where we live.” – Patient

“Access to trientine for my Wilson disease patients has been extremely difficult. I applied for reimbursement for my patient but it was turned down. I tried again and have been waiting months for a response. One of my patients has developed cirrhosis and we are now planning for a liver transplant. This is not acceptable. Wilson disease patients NEED quick and affordable access to treatment – their lives depend on it.” – Health professional

“As a liver specialist with many Wilson disease patients, I urge CADTH to recommend reimbursement for trientine in Canada. This has already been approved by Health Canada so it should essentially be available to Canadian patients, but without reimbursement, this treatment remains out of reach to Wilson disease patients. This systemic problem must be addressed in order to save lives.” – Health professional

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.**

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 survey.

- 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 outside assistance was utilized to collect or analyze data used in 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 survey.

- 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
N/A				

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: Nem Maksimovic
Position: Manager, National Health Promotion and Education
Patient Group: Canadian Liver Foundation
Date: July 23rd, 2021