

CADTH Reimbursement Recommendation

Trientine Hydrochloride (Waymade-Trientine)

Indication: For the treatment of patients with Wilson disease who are intolerant to penicillamine.

Sponsor: Waymade PLC

Final recommendation: Reimburse with conditions

ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

What Is the CADTH Reimbursement Recommendation for Waymade-Trientine?

CADTH recommends that Waymade-Trientine should be reimbursed by public drug plans for the treatment of patients with Wilson disease if certain conditions are met.

Which Patients Are Eligible for Coverage?

Waymade-Trientine should only be covered to treat patients who have previously tried and demonstrated intolerance to d-penicillamine (DPA).

What Are the Conditions for Reimbursement?

Waymade-Trientine should only be reimbursed if initiated by clinicians experienced in the management of Wilson disease and if the cost of Waymade-Trientine is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 study suggested that Waymade-Trientine had comparable efficacy to DPA in terms of liver and nervous system improvement. Also, Waymade-Trientine may be more tolerable than DPA.
- Due to limitations with the clinical evidence and economic model design, the cost-effectiveness of Waymade-Trientine relative to no treatment or to alternative therapies used to treat patients with Wilson disease is highly uncertain. Economic evidence from an exploratory analysis suggests that a price reduction of at least 46% is needed to ensure Waymade-Trientine is cost-effective at a \$50,000 per quality-adjusted life-year (QALY) threshold.
- Based on public list prices, Waymade-Trientine is expected to cost the public drug plans \$14,935,472 over 3 years.

Additional Information

What Is Wilson Disease?

Wilson disease is a rare genetic disease of copper metabolism that can involve the liver, nervous system, brain, or a combination of these. Wilson disease may lead to liver failure, movement disorders, intellectual deterioration, and may ultimately be fatal. Most patients with Wilson disease present between 5 and 35 years of age. Wilson disease has been estimated to affect 1 in 30,000 people.

Unmet Needs in Wilson Disease

There is a need for an effective and tolerable copper chelating drug for patients who cannot tolerate DPA and for patients in whom DPA should not be used.

How Much Does Waymade-Trientine Cost?

Treatment with Waymade-Trientine is expected to cost approximately \$21,900 to \$58,400 per adult patient per year, and \$14,600 to \$58,400 per child or adolescent patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that trientine hydrochloride be reimbursed for the treatment of patients with Wilson disease who are intolerant to penicillamine only if the conditions listed in Table 1 are met. As per the product monograph, Health Canada has not authorized trientine hydrochloride for use in children younger than 5 years of age.

Rationale for the Recommendation

One retrospective cohort study of patients with Wilson disease suggested that treatment with trientine hydrochloride had comparable efficacy to d-penicillamine (DPA). Specifically, hepatic improvement scores for all patients were comparable in the first-line treatments group (25 of 38 [65.8%] trientine treatments versus 185 of 295 [62.7%] DPA treatments), as well as the second-line treatments group (31 of 103 [30.1%] trientine treatments versus 12 of 31 [38.7%] DPA treatments). Similarly, neurologic improvement scores for all patients were comparable in the first-line treatments group (11 of 38 [28.9%] trientine treatments versus 77 of 295 [26.1%] DPA treatments) as well as the second-line treatments group (26 of 103 [25.2%] trientine treatments versus 3 of 31 [9.7%] DPA treatments). Further, trientine had improved tolerability compared with DPA. This was demonstrated by a lower number of treatments discontinued due to adverse events with trientine (10 of 141 [7.1%] treatments) versus DPA (94 of 326 [28.8%] treatments). The presented evidence was also considered in light of the lack of an effective option for patients who cannot tolerate DPA, and the high morbidity and mortality associated with the lack of treatment. Given the lack of other options for copper chelating agents, CDEC concluded that trientine met some of the needs identified by patients: specifically, the improved tolerability profile compared to DPA.

The cost-effectiveness of trientine is highly uncertain due to limitations with the economic model and clinical evidence. As such, a base-case cost-effectiveness estimate was unable to be determined in patients with Wilson disease who are intolerant to DPA. CDEC considered exploratory analyses conducted by CADTH where the incremental cost-effectiveness ratio (ICER) was \$146,927 per QALY when compared with no treatment and therefore determined that trientine would likely not be considered cost-effective at a \$50,000 QALY WTP threshold. Based on these reanalyses, a price reduction would be required for trientine to achieve an ICER of \$50,000 per QALY.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients eligible for reimbursement with trientine hydrochloride must have previously tried and demonstrated intolerance to DPA.	Health Canada indication specifies the use of trientine hydrochloride to patients who are intolerant to DPA.

Reimbursement condition	Reason
Prescribing	
2. For adult patients with Wilson disease, initiation, but not renewal, should be restricted to clinicians experienced in the management of Wilson disease.	For adults, clinical expertise is required to assess aspects of Wilson disease that require specialized knowledge, including intolerance of DPA and assessment of neurologic worsening. However, clinical experts indicated that specialized knowledge is not required for adult patients who are taking trientine hydrochloride and their disease is stable. In such cases, restricting renewal to clinical experts with specialized knowledge is not required and may impose burdens on patients.
3. For pediatric patients with Wilson disease, both initiation and renewal should be restricted to clinicians experienced in the management of Wilson disease.	In light of the limited safety and efficacy data in pediatric patients, clinical experts indicated that pediatric patients would benefit from continued monitoring by a clinician experienced in the management of Wilson disease.
Pricing	
4. A reduction in price	The cost-effectiveness of trientine is highly uncertain. Given the absence of evidence for key economic parameters, a CADTH base-case analysis could not be conducted. Exploratory analyses, which varied key parameters in the model, were conducted instead. These analyses indicated that a reduction in price is required to achieve an ICER of \$50,000 per QALY. It is likely that the price reduction will need to be greater than 46% to address the uncertainty in both clinical evidence and model design.
Feasibility of adoption	
5. The feasibility of adoption of trientine must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.

DPA = d-penicillamine; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance from CDEC

Condition no. in Table 1	Implementation considerations and guidance
1	Intolerance to DPA includes a wide range of adverse events. Defining criteria for intolerance can be addressed at the individual jurisdiction level in consultation with clinical experts. In addition, patients with a contraindication to DPA should not be excluded from reimbursement.

DPA = d-penicillamine.

Discussion Points

- The reviewed evidence does not support combining use of trientine with DPA or zinc. However, in practice, clinical experts suggested that zinc may sometimes be used in combination with trientine hydrochloride.
- In Canada, trientine has been available for patients with Wilson disease through various compassionate and special access programs (SAPs). Over the past 3 decades, there has been an established clinical experience using trientine for the treatment of patients with Wilson disease.
- CADTH previously reviewed Mar-Trientine, another trientine product indicated for the treatment of Wilson disease, which was submitted at the same unit price as Waymade-Trientine. While both models considered similar inputs and the same body of evidence on the safety and efficacy of trientine, the Mar-Trientine submission was based on a decision tree model while Waymade-Trientine was based on a Markov model. Given the modelling approach taken in the Waymade-Trientine submission was more appropriate to fit the decision problem, the ICER and subsequent price reduction required to achieve an ICER of \$50,000 per QALY is likely closer to that predicted in the CADTH exploratory analysis with Waymade-Trientine. Additionally, CDEC notes that there is no evidence to support a price premium for Waymade-trientine over Mar-trientine, or the other way around.
- Patients indicated that drug refrigeration is a relevant factor that affects day-to-day activity. The drug formulation in the present recommendation (Waymade-trientine) does not address this need. However, CDEC noted that there is lack of evidence as to the effect of refrigeration on health-related quality-of-life measures in patients with Wilson disease who are treated with trientine.

Background

Trientine hydrochloride has a Health Canada indication for the treatment of patients with Wilson disease who are intolerant to penicillamine. Trientine hydrochloride is a chelating agent with a polyamine-like structure that chelates copper by forming a stable complex with the 4 constituent nitrogens in a planar ring that is readily excreted in the urine. Trientine hydrochloride is available as 250 mg oral capsules.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of the 1 retrospective cohort study of patients with Wilson disease.
- Patients' perspectives gathered by 1 patient group, The Canadian Liver Foundation.
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- Two clinical specialists with expertise diagnosing and treating patients with Wilson disease.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient submission from the Canadian Liver Foundation (CLF) was received for this drug. The CLF supports education and research into all forms of liver diseases and is committed to reducing the incidence and impact on Canadians at risk or living with liver diseases. The CLF gathered information through an online survey to which 8 patients and 5 caregivers responded, although additional input was collected from 2 health care professionals.

Patients described the negative impact of Wilson disease on their day-to-day activities, which was reiterated by caregivers, related especially to the ability to work and travel. The emotional and psychological effects of living with and managing Wilson disease results in constant stress and fear as well as psychiatric symptoms such as anxiety and depression, which negatively affect patient and caregiver quality of life. Side effects of current treatments such as fatigue, appetite loss, nausea, and pain were described as completely to somewhat intolerable. The survey respondents felt it was important to have access and choice of treatments for Wilson disease and for choices to be based on known side effects. The following outcomes were identified as being important to patients: reduction of short- and long-term side effects, overall quality of life, long-term disease stability, and adherence. Two patients and 2 caregivers had experience with trientine and relayed the challenges of accessing trientine via the SAP and obtaining private insurance coverage for it. If unable to access trientine, patients may have no choice but to use DPA despite experiencing side effects because they require chelation therapy to live. A benefit of trientine that was highlighted by patients was that it does not require refrigeration, thus making it more portable.

The responses from the 2 health care professionals firmly advocated for better access to medications for their patients with Wilson disease and described the difficulty in accessing trientine for their patients. Moreover, without reimbursement, trientine remains out of reach for many patients with Wilson disease, which is unacceptable in their views because these patients require effective and safe chelation therapy to live.

Clinician Input

Two clinical specialists with expertise in the diagnosis and management of Wilson disease in adult and pediatric patients, respectively, contributed to this review. The clinicians advised that not all patients will respond to, or tolerate, DPA or zinc. Further, Canadian patients who require chelation and cannot take DPA due to toxicity or intolerance (estimated to be 20% to 40% of patients) currently have no available chelation treatment options as in the expert's experience, zinc is inadequate in about 30% of patients and is relatively poorly tolerated. Available treatments have limited effect on acute liver failure, and none can reverse the neurologic or psychiatric manifestations of Wilson disease. A specific unmet need identified by the pediatric clinical expert was the lack of specific drug formulations (e.g., liquid formulations) to meet pediatric needs.

The current use of trientine after DPA treatment is mainly due to access issues. In the clinical expert's opinion, if trientine were available as a first-line option, it would be preferred by many providers due to twice daily dosing, few adverse events (AEs), good tolerability, and solid efficacy. The clinical experts felt it was inappropriate for trientine to be limited only to patients who do not tolerate or fail DPA or zinc; however, if DPA and/or zinc must be tried before access to trientine is granted, intolerance or lack of efficacy should be based on subjective

inability to tolerate the medication (AEs), poor adherence, and/or lack of efficacy based on symptom progression and/or inadequate de-coppering measured by non-ceruloplasmin-bound copper or 24-hour urinary copper excretion. Repeated trials of DPA or zinc should not be required before granting approval for trientine as toxicity with DPA may be worse upon rechallenge and some AEs associated with DPA are irreversible or slow to reverse and may be difficult, if not impossible, to predict. Significant delays in initiating therapy in patients with progressive disease can lead to irreversible impairment and this is particularly true with neurologic symptoms associated with Wilson disease.

The clinical experts advised that any patient with Wilson disease is expected to respond to trientine in terms of reducing overall body copper burden. Both adult and pediatric patients with hepatic-prominent Wilson disease are likely to have their hepatic symptoms respond to chelation therapy, including trientine. In contrast, patients with neurologic disease may have their neurologic symptoms worsen with initiation of any chelator treatment due to too rapid cerebral mobilization of copper.¹² Some evidence and anecdotal reports suggest that neurologic worsening occurs more frequently with DPA than trientine, although this has not been rigorously evaluated. The experts felt that patients with advanced and progressive neurologic and/or psychiatric disease would be considered least suitable for trientine treatment, although trientine may still stabilize the disease and prevent further progression. Patients with acute liver failure often require immediate liver transplantation so trientine is unlikely to benefit those presenting with an acute Wilsonian crisis. Patients without symptoms but a confirmed diagnosis of Wilson disease should be treated; however, if the copper burden is not excessive initial treatment with zinc is appropriate rather than chelation therapy.

According to the clinical experts, response to treatment is usually assessed by ceruloplasmin-bound copper, 24-hour urinary copper collection, as well as liver enzymes and function tests in both adult and pediatric patients. It is also important to assess neurologic and hepatic improvement following treatment. While some assessments are subjective, they can usually be supported by objective assessments. Treatment response should be subjectively evaluated (i.e., patient perspective on symptoms) monthly at treatment initiation and then every 6 to 12 months once stable. Objective assessments such as neurologic assessment with or without brain MRI, laboratory improvement (non-ceruloplasmin-bound copper, 24-hour urinary copper excretion, liver enzymes/function) should be evaluated at least annually but may require more frequent testing, especially at treatment initiation. In pediatric patients, response to treatment should be assessed more frequently (e.g., every 3 to 6 months) due to the need for more frequent reassessment of dosage and treatment efficacy because of weight-based dosing.

The clinical experts reiterated that treatment of Wilson disease is lifelong and in all cases if 1 chelator is stopped, an alternative treatment must be started immediately as patients cannot be left untreated. The main reason for treatment discontinuation would be inadequacy of treatment due to either lack of efficacy or tolerability issues. The experts agreed that while a specialist is required to diagnose Wilson disease and should be involved in the care of patients, they do not necessarily have to be the only prescriber of trientine. Once a diagnosis is established, patients can be followed locally because access to a specialty clinic or specialist with experience treating Wilson disease could be problematic for patients.

Drug Program Input

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Clinicians may wish to access trientine before DPA due to its better tolerability profile. Is it reasonable to allow use as first-line and if so, what criteria should apply?	Input from clinical experts and available evidence suggests that first-line therapy with trientine hydrochloride may be reasonable. However, considering the many limitations in the available evidence as well as the indication from Health Canada, it is appropriate to restrict trientine hydrochloride as a second-line therapy.
Trientine is only approved for use in children ≥ 5 years of age. Clinicians may wish to use trientine in children < 5 years of age. Should this be allowed and if so, what criteria should apply?	Input from clinical experts suggests that there is no a priori biological reason to expect trientine hydrochloride to be less effective in children under 5 years of age. However, the clinical experts indicated that dosage challenges exist in the current available formulation of trientine hydrochloride. The evidence reviewed by CDEC did not provide results on efficacy and safety of trientine hydrochloride in children less than 5 years of age. Considering this limitation in the evidence, along with the indication from Health Canada, CDEC recommend restricting the use of trientine hydrochloride to patients 5 years of age or older.
The product monograph states that trientine should only be initiated by physicians experienced in the management of Wilson disease. How are these physicians identified? Do all jurisdictions have access to physicians with experience treating Wilson disease?	Diagnosis, treatment initiation, and treatment switching should be conducted by clinicians with experience in managing Wilson disease. Considering the rarity of the disease there are few specialty clinics available. Renewal of treatment in adults with a stable condition should not require a clinical expert. Treatment monitoring should be instructed by a clinician with experience in managing Wilson disease. However, pediatric patients should be followed by pediatric clinician experts given the uncertainties related to efficacy and safety in that population.
Considerations for discontinuation of therapy	
A definition of intolerance to d-penicillamine would be helpful.	Defining criteria for intolerance can be addressed at the individual jurisdiction level in consultation with clinical experts. Intolerance or lack of efficacy can be based on subjective inability to tolerate the medication, AEs, poor adherence, and/or lack of efficacy based on symptom progression and/or inadequate de-coppering measured by non-ceruloplasmin-bound copper or 24-hour urinary copper excretion.
Considerations for prescribing of therapy	
Should prescribing be restricted only to certain specialties (e.g., gastroenterologists, hepatologists, internal medicine) or all practitioners?	Treatment initiation and switching should be restricted to clinicians with experience in managing Wilson disease. Renewal in adult patients with a stable condition should not require such a restriction. In pediatric patients, initiation, switching, and renewal should all be restricted to clinicians with experience in managing Wilson disease.
Criteria for Waymade-Trientine should be consistent with what is recommended for Mar-Trientine.	CDEC acknowledges the statement from the drug programs.

AE = adverse Events; CDEC = Canadian Drug Expert Committee.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two pivotal trials submitted by the sponsor were included in the systematic review. No additional trials from the literature search met the inclusion criteria for the systematic review and no indirect comparisons or other relevant evidence were identified. The first included study (Weiss et al., 2013) was a retrospective cohort analysis that evaluated the efficacy and safety of trientine compared to DPA in 405 patients with Wilson disease based on hepatic and neurologic outcomes and treatment discontinuations due to AEs. The analysis included 380 patients who were examined at tertiary care centres in Germany (Heidelberg, Dresden, and Dusseldorf) and Austria (Vienna, Graz, and Linz) and 25 additional patients identified from the EUROWILSON registry who had received trientine monotherapy. There were no patient inclusion criteria stated and no information on the specific time frame of the study or the calendar years over which time the patients were treated. It appears that efficacy outcomes were based on the latest available follow-up evaluation within a 6- to 48-month period. Data on discontinuations and discontinuations due to AEs were collected over a median 13.3-year period, although no range of time was reported. The results of the analysis were reported by number of chelator treatments (i.e., 326 DPA treatments and 141 trientine treatments) rather than by the number of patients, and the researchers categorized the DPA and trientine treatments as first-line or second-line, but how this was determined is unknown. The second study (Study 17-VIN-0021) was an open-label, 2-period, 2-sequence, 2-treatment, crossover, single-dose, fasting bioequivalence study of Waymade-Trientine 250 mg capsules compared to Syprine 250 mg capsules in 44 healthy adult male volunteers. The objective of this study was to compare the rate and extent of absorption of trientine from the 2 formulations to determine if they were bioequivalent. As the purpose of Study 17-VIN-0021 was to assess bioequivalence in healthy volunteers and not the efficacy and safety of trientine in patients with Wilson disease, this study was not reviewed in detail in this report.

According to the clinical experts on the review team, the baseline characteristics of the patients in the Weiss et al., 2013 study are reasonably similar to Canadian patients who would be candidates for trientine, with the possible exception of pediatric patients (< 18 years of age). The median age of included patients at the time of diagnosis of Wilson disease (the only age parameter reported in the study) was 17 to 19 years. Although patients less than 18 years were included, no details on the number or the age of pediatric patients was provided. At initial presentation, about half (207 [51.1%] patients) had only hepatic symptoms, 92 (22.7%) had only neurologic symptoms, 52 (12.8%) had mixed presentation (hepatic and neurologic symptoms), and 54 (13.3%) were asymptomatic, a similar distribution as expected in Canadian clinical practice.

Efficacy Results

Hepatic Impairment

In the Weiss et al., 2013 study, hepatic improvement scores after first-line treatment were comparable for all patients (25 of 38 [65.8%] trientine treatments versus 185 of 295 [62.7%] DPA treatments) and for symptomatic patients (25 of 27 [92.6%] versus 185 of 204 [90.7%], respectively) which were not statistically significantly different. Following second-line treatment, hepatic improvement scores were generally lower than with first-line treatment (i.e., 31 of 103 [30.1%] trientine treatments and 12 of 31 [38.7%] DPA treatments) for all

patients and (31 of 45 [68.9%] and 12 of 16 [75.0%], respectively) for symptomatic patients. There were also no statistically significant differences between treatments. For symptomatic patients, stable hepatic disease categorized as unchanged hepatic symptoms was observed in 7.4% of first-line treatments for both groups (i.e., 2 of 27 trientine treatments and 15 of 204 DPA treatments). Stable hepatic disease after second-line therapy was reported in 10 of 24 (22.2%) of trientine treatments and 4 of 16 (25%) of DPA treatments. No statistical comparisons were reported for the number of treatments associated with stable or unchanged hepatic symptoms.

There were no first-line trientine treatments associated with hepatic worsening (i.e., defined as a decline in liver function or progression of chronic liver disease) compared to first-line DPA treatments (i.e., 0 of 38 [0%] trientine treatments versus 4/295 [1.4%] DPA treatments) for all patients and (0 of 27 (0%) versus 4 of 204 (2.0%), respectively) for symptomatic patients. While second-line trientine treatment was associated with hepatic worsening, there were no second-line DPA treatments associated with hepatic worsening (i.e., 4 of 103 [3.9%] trientine treatments versus 0 of 31 [0%] DPA treatments) for all patients and (4 of 45 [8.9%] versus 0 of 16 [0.0%], respectively) for symptomatic patients. The differences between trientine and DPA treatments for hepatic worsening after either first-line or second-line treatments were not statistically significantly different. Overall, there were 12 treatments with an outcome of liver transplantation (i.e., 3 [2.1%] trientine treatments and 9 [2.7%] DPA treatments).

Neurologic Impairment

In the Weiss et al., 2013 study, neurologic improvement scores for first-line treatment were comparable between trientine treatments (11 of 38 [28.9%]) and DPA treatments (77 of 295 [26.1%]) for all patients but were numerically higher for DPA treatments (77 of 114 [67.5%]) versus trientine treatments (11 of 20 [55.0%]) in symptomatic patients, although the differences were not statistically significant. Following second-line therapy for all patients, neurologic improvement rates were comparable to those after first-line therapy for trientine treatments (26 of 103 [25.2%]) but were numerically lower for DPA treatments (3 of 31 [9.7%]). For symptomatic patients, neurologic improvement with second-line therapy after trientine treatments (26 of 51 [51.0%]) was numerically higher than after DPA treatments (3 of 13 [23.1%]). Nonetheless, all comparisons between trientine and DPA treatments for all patients and symptomatic patients for second-line therapy were not statistically significantly different. For symptomatic patients, stable neurologic disease, which was categorized as unchanged neurologic symptoms, was observed in 5 of 20 (25.0%) trientine treatments and 31 of 114 (27.2%) DPA treatments after first-line therapy and 1 of 51 (33.3%) and 9 of 13 (69.2%), respectively, after second-line therapy. No statistical comparisons were reported for stable or unchanged neurologic symptoms.

Rates of neurologic worsening after first-line therapy were statistically significantly higher for trientine treatments compared to DPA treatments for all patients (4 of 38 [10.5%] versus 6 of 295 [2.0%]; $P = 0.018$) and for symptomatic patients (4 of 20 [20.0%] and 6 of 114 [5.3%]; $P = 0.042$), respectively. For second-line therapy, rates of neurologic worsening were numerically higher with trientine treatments compared to DPA treatments for all patients (8 of 103 [7.8%] and 1 of 31 [3.4%], respectively) and symptomatic patients (8 of 51 [15.7%] and 1 of 13 [7.3%], respectively); although the differences were not statistically significant.

Harms Results

In the Weiss et al., 2013 study, the only harms outcomes reported were the proportions of chelator treatments with AEs that led to treatment discontinuation. Treatment

discontinuations due to AEs were more common with DPA (94 of 326 [28.8%] treatments) compared with trientine (10 of 141 [7.1%] treatments). The difference between DPA and trientine treatments was statistically significant ($P = 0.039$), as reported in the publication.¹³ The frequency of AEs was higher with DPA treatments and the most common AEs ($\geq 5\%$ frequency in either group) that led to treatment discontinuation were arthralgia (29 of 326 [8.9%] versus 4 of 141 [2.8%]), increase in antinuclear antibodies (22 of 326 [6.7%] versus 1 of 141 [0.7%]), and albuminuria/proteinuria (20 [6.1%] versus not reported) for DPA treatments versus trientine treatments, respectively. Rates of discontinuations for any reason were not statistically significantly different between the chelator treatments ($P = 0.360$), as reported in the publication.

Critical Appraisal

Key limitations of the Weiss et al., 2013 study pertaining to internal validity are the retrospective design, which is limited by lack of randomization and the non-prospective collection of efficacy and harms outcomes, and the unknown time frame of the study. The analysis was also not blinded which may have introduced bias into the categorization of hepatic and neurologic outcomes and the identification of symptomatic patients, as all were subjectively assessed by the researchers. The reporting of results by number of chelator monotherapy treatments rather than by number of patients complicates the interpretation of baseline characteristics and efficacy and harms outcomes as an individual patient may have been counted more than once in the results. This leads to double data counting which compromises the validity of the dataset. For example, if an individual patient displays a specific characteristic such as hepatic presentation, this will result in more treatments being characterized as having hepatic presentation than if patients were randomly selected and counted only once in the dataset. There were no clear definitions or validation of the efficacy outcomes in terms of reliability, validity, responsiveness, or minimally important differences, which makes interpretation difficult.

Key limitations relating to external validity in the Weiss et al., 2013 study are the lack of data for Canadian patients, lack of evidence on combination use of trientine in combination with zinc which is common in clinical practice, and lack of evidence in pediatric patients. The diagnosis and treatment of Wilson disease can be challenging in children as children may not display the same clinical and laboratory hallmarks of the disease as adults. No information on the dosage and administration schedules of trientine or DPA used in the study were reported so it is not known if the dosage regimens used in the study are in alignment with the Health Canada–approved doses for trientine and DPA. There were also no data available for most efficacy outcomes identified in the review protocol, including outcomes of interest to patients such as health-related quality of life and adherence.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with Wilson disease who are intolerant to DPA
Treatment	75 mg daily oral zinc, followed by trientine (1,000 mg daily) for patients who did not achieve stable hepatic symptoms on zinc
Submitted price	Trientine hydrochloride 250 mg: \$20.00 per capsule
Treatment cost	The annual cost of therapy ranges \$21,900 to \$58,400 for adult patients, \$14,600 to \$58,400 for adolescents aged 13 to 17 years, and \$14,600 to \$43,800 for children aged 5 to 12 years.
Comparator	75 mg daily oral zinc, followed by no treatment for patient who did not achieve stable hepatic symptoms on zinc
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (68 years)
Key data source	Retrospective cohort studies conducted by Weiss et al.
Submitted results	For zinc followed by trientine compared to zinc followed by no treatment: ICER = \$54,967 per QALY (\$322,049 incremental costs, 5.86 incremental QALYs)
Key limitations	<ul style="list-style-type: none"> • No treatment is unlikely to represent the current standard of care. • Clinical evidence regarding the efficacy and tolerability of trientine is limited due to the lack of randomized trials. • The proportion of patients who will progress to advanced liver disease, liver transplant, or death is uncertain. • The modelled population is not consistent with that of the Health Canada indication or reimbursement request. Trientine is indicated for second-line therapy after DPA rather than third line therapy after DPA and zinc. • The model does not consider the neurologic and psychological symptoms associated with Wilson disease. • A single treatment decision and 100% adherence do not reflect the management of Wilson disease in clinical practice. • Modelled costs and utilities did not change over time, whereas utilities tend to decrease as people age and post-liver transplant costs are not static over time. • Health state utilities values are uncertain. • The mean starting age of patients in the model did not reflect the age at which patients are diagnosed and treatment begins. • The mean dose of trientine that will be used in clinical practice is uncertain.

Component	Description
CADTH reanalysis results	<ul style="list-style-type: none"> • Due to the extent of uncertainty in the model, a CADTH base case could not be derived. • In an exploratory reanalysis CADTH: removed zinc from the treatment paradigm, lowered the age of patients entering the model, reduced the rate at which patients with worsening symptoms progress to ALD, reduced the rate at which patients in ALD die, and increased the proportion of patients in ALD who receive a liver transplant. • CADTH reanalyses greatly increased the costs associated with treatment with trientine, but also increased the associated QALYs. The model was most sensitive to changes in the proportion of patients who progress to advanced liver disease. • CADTH’s exploratory analyses estimated that the ICER associated with trientine was \$146,927 per QALY when compared to no treatment (\$694,602 incremental costs, 4.73 incremental QALYs). At this ICER, a 46.5% price reduction would be required to achieve an ICER below \$50,000 per QALY. • CADTH was unable to address the absence of symptoms in the model, the lack of an active comparator, or the increased risks associated with nonadherence. • CADTH previously reviewed Mar-Trientine, another trientine product indicated for the treatment of Wilson disease, which was submitted at the same unit price as Waymade-Trientine and had the same safety and efficacy data but used a different modelling approach. As such, uncertainties within the clinical evidence and other inputs had different impacts on each model. In both cases, CADTH was unable to determine a base-case analysis and provided exploratory analyses leading Mar-Trientine to be associated with an ICER of \$87,676 per QALY and Waymade-Trientine being associated with an ICER of \$146,927 per QALY. This difference should not be interpreted as a difference in the true cost-effectiveness of Waymade-Trientine compared to that of Mar-Trientine but rather in a difference in the modelling approach.

ALD = advanced liver disease; DPA = d-penicillamine; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor’s analysis:

- The population who will be eligible for chelation therapy was underestimated.
- Funding previously spent on trientine through the SAP program was not considered.
- Downstream medication costs were not considered.
- The proportion of patients who would be eligible for public reimbursement was underestimated.
- Some eligible patients may not switch to trientine in the first year of reimbursement.
- Adherence rates are highly uncertain, and their inclusion likely underestimates drug costs.
- Copayments were insufficiently modelled and inappropriate in the base case.

CADTH reanalyses included: removing copays from consideration, increasing the proportion of patients who require chelation therapy, increasing the proportion of patients who will be eligible for public reimbursement, and assuming 100% adherence.

Based on CADTH reanalyses, the budget impact of reimbursing trientine for patients who are intolerant to DPA is expected to be \$5,191,012 in year 1, \$5,259,144 in year 2, and \$5,327,301 in year 3, for a 3-year total budget impact of \$15,777,456 (\$14,935,472 when dispensing fees and markups are excluded). This estimate was substantially different from that of the sponsor (3-year total: \$3,844,144). CADTH was neither able to account for the offsetting of medications required for the hepatic and neurologic consequences of unstable Wilson disease, nor for the funding previously spent to acquire trientine through the SAP; thus, the actual budgetary impact of reimbursing trientine is likely lower than estimated.

CDEC Information

CDEC Members

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: December 15, 2021.

Regrets: One expert committee member did not attend.

Conflicts of interest: None.