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CADTH Reimbursement Recommendation

Trientine Hydrochloride (MAR-Trientine)

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

Sponsor: Marcan Pharmaceuticals Inc.

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for MAR-Trientine?

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

Which Patients Are Eligible for Coverage?

MAR-Trientine should only be covered to treat patients who have previously tried and demonstrated intolerance to d-penicillamine.

What Are the Conditions for Reimbursement?

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

Why Did CADTH Make This Recommendation?

- Evidence from 1 study suggested that MAR-Trientine had comparable efficacy to d-penicillamine (DPA) in terms of liver and nervous system improvement. Also, MAR-Trientine may be more tolerable than DPA.
- The cost-effectiveness of MAR-Trientine is highly uncertain due to limitations with the economic model and clinical evidence. Based on exploratory analyses, MAR-Trientine is not considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) for patients included in the indication approved by Health Canada, relative to no treatment. A price reduction is therefore required.
- Economic evidence from an exploratory analysis suggests that a 27% price reduction is needed to ensure MAR-Trientine is cost-effective at a $50,000 per QALY threshold.
- Based on public list prices, MAR-Trientine is expected to cost the public drug plans $12,958,161 over 3 years.

Additional Information

What Is Wilson's Disease?

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

Unmet Needs in Wilson's Disease

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

How Much Does MAR-Trientine Cost?

Treatment with MAR-Trientine is expected to cost approximately $21,900 to $58,400 per adult patient per year depending on what dose is given. In adolescent patients (aged 13 to 17) this range falls to $14,600 to $58,400 and in patients under the age of 13 the range falls to $14,600 to $43,800. The differences in ranges represents different maximum and minimum dosages.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that trientine hydrochloride be reimbursed for the treatment of of patients with Wilson's 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's disease suggested that treatment with trientine hydrochloride had comparable efficacy to 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 drugs, 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's disease who are intolerant to DPA. The committee considered exploratory analyses conducted by CADTH where the incremental cost-effectiveness ratio (ICER) was $87,676 per QALY and therefore determined that MAR-Trientine would likely not be considered cost-effective at a $50,000 per QALY WTP threshold. Based on these exploratory analyses, a price reduction would be required for MAR-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 hydrocholoride to patients who are intolerant to DPA.

Reimbursement condition	Reason
Prescribing	
2. For adult patients with Wilson's disease, initiation, but not renewal, should be restricted to clinicians experienced in the management of Wilson's disease.	For adults, clinical expertise is required to assess aspects of Wilson's 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's disease, both initiation and renewal should be restricted to clinicians experienced in the management of Wilson's 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's disease.
Pricing	
4. A reduction in price	The cost-effectiveness of trientine hydrochloride 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 26% to address the uncertainty in both clinical evidence and model design.

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	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.

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's disease through various compassionate and special access programs. During the past 3 decades, there has been an established clinical experience using trientine for the treatment of patients with Wilson's disease.

Background

Trientine hydrochloride has a Health Canada indication for the treatment of patients with Wilson's disease who are intolerant to penicillamine. Trientine hydrochloride is a chelating drug 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, CDEC considered the following information:

- A review of the 1 retrospective cohort study of patients with Wilson's disease.
- Patients' perspectives gathered by 1 patient group, The Canadian Liver Foundation (CLF).
- 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's disease.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient submission from CLF was received for this review. 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's disease on their day-to-day activities which was reiterated by caregivers, especially regarding the ability to work and travel. The emotional and psychological effects of living with and managing Wilson's 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's 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 Special Access Programme (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. Another benefit of trientine 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's disease and described the difficulty in accessing trientine for their patients. Moreover, without reimbursement, trientine remains out of reach for many patients with Wilson's 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's 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's 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's disease.

The clinical experts advised that any patient with Wilson's disease is expected to respond to trientine in terms of reducing overall body copper burden. Both adult and pediatric patients with hepatic-prominent Wilson's 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's 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's disease is life-long 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's 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's disease could be problematic for patients.

The clinical experts described the current situation with trientine in Canada as a risk to achieving desired patient outcomes. The approval of MAR-Trientine by Health Canada led to immediate suspension of the SAP without a plan in place to provide trientine to Canadian patients who were on treatment with imported product. This led to almost immediate loss of access to trientine, interruptions in treatment, and great anxiety for patients and providers. The clinical experts advocated for an improved process for bridging patients who are receiving a medication through the SAP to be able to retain access to the medication throughout the Health Canada approval and drug reimbursement review processes.

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 biologic 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's disease. How are these physicians identified? Do all jurisdictions have access to physicians with experience treating Wilson's disease?	Diagnosis, treatment initiation, and treatment switching should be conducted by clinicians with experience in managing Wilson's 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's disease. However, pediatric patients should be followed by pediatric clinician experts given the uncertainties related to efficacy and safety in that population.
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's 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's disease.

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's 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 16-VIN-0315) was an open-label, 2-period, 2-sequence, 2-treatment, crossover, single-dose, fasting bioequivalence study of MAR-Trientine 250 mg capsules compared to Syprine (trientine) 250 mg capsules in 36 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 16-VIN-0315 was to assess bioequivalence in healthy volunteers and not the efficacy and safety of trientine in patients with Wilson's 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's 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 (Table 2). 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 of 295 [1.4%] DPA treatments) for all patients and (0 of 27 [0%] versus 4 of 204 [2.0%], respectively) for symptomatic patients. (Table 2). 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 [0.0%] 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 (77/295 [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 (Table 2). 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 5/20 (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 (Table 2). 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) (Table 2). 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 (5% or higher 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 or 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's disease can be challenging in children as children may not display the same clinical and laboratory hallmarks of the disease as adults.[14] 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 Decision tree
Target population	Patients with Wilson's disease who are intolerant to DPA
Treatment	75 mg daily oral zinc for 6 months, followed by trientine (1,000 mg daily) for patients who did not achieve stable hepatic symptoms on zinc
Submitted price	$20.00 per 250 mg capsule
Treatment cost	Adult: $21,900 to $58,400 per year Adolescent (13 to 17): $14,600 to $58,400 per year Child (5 to 12): $14,600 to $43,800 per year

Component	Description
Comparator	75 mg daily oral zinc for 6 months, followed by no treatment for patient who did not achieve stable hepatic symptoms on zinc
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (41 years)
Key data source	Retrospective cohort studies conducted by Weiss et al.
Key limitations	• No treatment is likely not the current standard of care. • Clinical evidence regarding the efficacy and tolerability of trientine is limited due to the lack of randomized trials. • 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's disease. • A single treatment decision and 100% adherence does not reflect the management of Wilson's disease in clinical practice. • The mean starting age of patients in the model (start age) is too old to reflect the age at which patients are diagnosed and treatment begins. • The proportions of patients who do not improve with treatment who would experience acute liver failure and then receive a liver transplant are uncertain. • The health state utility values are uncertain. • The impact of acute liver failure and liver transplant surgery on quality of life were not considered.
CADTH reanalysis results	• In an exploratory reanalysis CADTH: removed zinc from the treatment pathway, lowered the age at which patients enter the model, lowered the proportion of patients who experience acute liver failure, and increased the proportion of patients 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 experience liver failure. • CADTH's exploratory analyses estimated that the ICER associated with trientine was $87,676 per QALY when compared to no treatment ($682,754 in incremental costs, 7.79 incremental QALYs). At this ICER a 27% price reduction would be required to achieve an ICER below $50,000 per QALY. • CADTH was unable to address the absence of neurologic symptoms in the model, the increased risks associate with nonadherence, or the impact of acute liver failure or transplantation surgery on quality of life.

Budget Impact

CADTH reanalysis of the sponsor's budget impact analysis (BIA) included: using an epidemiological approach to estimate the number of patients in Canada with Wilson's disease who will be eligible for trientine therapy, and increasing the proportion of patients who are eligible for public drug plan coverage.

Based on CADTH reanalyses, the budget impact of reimbursing trientine for patients who are intolerant to DPA is expected to be $2,780,886 in year 1, $4,496,691 in year 2, and $5,680,583 in year 3, for a 3-year total budget impact of $12,958,161 ($13,681,776 when dispensing fees and markups are included). CADTH was unable to account for the offsetting of medications

required for the hepatic and neurologic consequences of unstable Wilson's disease, or for the funding previously spent to acquire trientine through the SAP program, thus the actual budgetary impact of reimbursing trientine may be lower than estimated.

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: September 22, 2021

Regrets: Two of the expert committee members did not attend

Conflicts of interest: None