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CADTH Reimbursement Review

Trientine Hydrochloride (Waymade-Trientine)

Sponsor: Waymade PLC

Therapeutic area: Wilson disease

Clinical Review
Pharmacoeconomic Review

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.

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Abbreviations

AE	adverse event
CLF	Canadian Liver Foundation
DPA	d-penicillamine
HRQoL	health-related quality of life
MID	minimal important difference
SAP	Special Access Program

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Wilson disease is a rare, heterogenous autosomal recessive disease of copper metabolism that can present with hepatic, neurologic, or psychiatric involvement (or a combination of these). It can also be asymptomatic.[1,2] Most patients with Wilson disease present between 5 years and 35 years of age. In children and younger adults, the disease presentation is mainly hepatic; neurologic manifestations tend to occur later, as copper accumulates in the body.[3-6] The global prevalence of Wilson disease has been estimated to be 1 in 30,000 in most populations, with a carrier gene frequency of 1 in 90 to 150 in the general population.[7,8]

Clinical manifestations of Wilson disease vary widely. Liver presentations can range from asymptomatic enzyme elevations to fulminant hepatic failure and other liver sequelae.[1] Neurologic symptoms include movement disorders or rigid dystonia. Psychiatric presentations may include depression, neurotic behaviour, or intellectual deterioration.[1] Kayser-Fleisher rings, which are yellow-brown discolourations of the cornea due to copper deposition, occur in 80% of all cases of Wilson disease.[4] A diagnosis is most often made by biochemical findings which — if observed in combination with low levels of ceruloplasmin (the major carrier for circulating copper in the blood), Kayser-Fleisher rings, and clinical signs — is usually definitive for Wilson disease, which is ultimately confirmed by molecular genetic testing.[1,3] The mainstays of treatment are dietary copper restriction, chelation therapy with either d-penicillamine (DPA) or trientine, and zinc salts.[3] Limitations associated with chelation therapy include the persistence or deterioration of neurologic symptoms (which may be irreversible) and intolerance to DPA in 20% to 40% of patients.[9] Zinc therapy is associated with nausea and gastritis, which may be due to the salt form used.[3,10] Treatment regimens for Wilson disease are complex and burdensome for patients because they require multiple dosing regimens appropriately spaced over the course of each day with regard to food and concomitant medication.[9] Problems with adherence are observed in almost half of all patients with Wilson disease, which is a key concern given that treatment is lifelong.[9] Untreated Wilson disease is ultimately fatal.[10]

Trientine is an oral copper-chelating drug that forms a stable copper complex that is readily excreted in the urine.[11] Waymade- Trientine (trientine hydrochloride) is available as 250 mg

Table 1: Submitted for Review

Item	Description
Drug product	Trientine hydrochloride (Waymade-Trientine), 250 mg capsules, oral
Indication	For the treatment of patients with Wilson disease who are intolerant to penicillamine
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	April 20, 2021
Sponsor	Waymade PLC

NOC = Notice of Compliance.

oral capsules and is approved by Health Canada for the treatment of patients 5 years of age and older with Wilson disease who are intolerant to penicillamine.[11] The sponsor has requested reimbursement as per the indication.

The objective of this systematic review is to evaluate the beneficial and harmful effects of trientine hydrochloride 250 mg oral capsules for the treatment of Wilson disease in patients who are intolerant to penicillamine.

Stakeholder Perspectives

The information in this section is a summary of input provided by 1 patient group that responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

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 disease and is committed to reducing the incidence and impact on Canadians who are at risk of or living with liver disease. The CLF gathered information through an online survey to which 8 patients and 5 caregivers responded. Additional input was collected from 2 health care professionals.

Patients described the negative impacts of Wilson disease on their day-to-day activities. Caregivers reiterated these impacts, especially regarding the ability to work and travel. The emotional and psychological effects of living with and managing Wilson disease result in constant stress, fear, and psychiatric symptoms, such as anxiety and depression, that negatively affect patient and caregiver quality of life. The side effects of current treatments, such as fatigue, appetite loss, nausea, and pain, were described as completely to somewhat intolerable. The survey respondents felt that it was important to have access to and choice in treatments for Wilson disease and for the choices to be based on known side effects. The following outcomes were identified as 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 who had experience with trientine relayed the challenges involved in accessing it through the Health Canada Special Access Program (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 highlighted by patients was that it does not require refrigeration, so is more portable.

The 2 health care professionals advocated firmly for better access to medications for their patients with Wilson disease and described the difficulty these patients have in accessing trientine. Without reimbursement, trientine remains out of reach for many patients with Wilson disease. From the health care professionals' perspectives, this is unacceptable because these patients require effective, 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 (an estimated 20% to 40% of patients) currently have no available chelation treatment options, given that, in the experts'

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 a specific drug formulation to meet pediatric needs (e.g., a liquid formulation).

Currently, the use of trientine after DPA treatment is due mainly to access issues. In the clinical experts' opinions, if trientine were available as a first-line option, it would be preferred by many providers due to its twice-daily dosing, few adverse events (AEs), good tolerability, and solid efficacy. The clinical experts believed that it was inappropriate for trientine to be limited 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, then intolerance or lack of efficacy should be based on subjective inability to tolerate the medication (i.e., AEs), poor adherence, and/or lack of efficacy based on symptom progression and/or inadequate de-coppering as 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 because 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. This is particularly true of the neurologic symptoms associated with Wilson disease.

The clinical experts advised that all patients with Wilson disease are 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 overly rapid cerebral mobilization of copper.[12] Some evidence and anecdotal reports suggest that neurologic worsening occurs more frequently with DPA than with trientine, although this has not been evaluated rigorously. The experts believed 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; as a result, trientine is unlikely to benefit those presenting with an acute Wilsonian crisis. Patients without symptoms who have a confirmed diagnosis of Wilson disease should be treated; however, if the copper burden is not excessive, then initial treatment with zinc is appropriate rather than chelation therapy.

According to the clinical experts, response to treatment in both adult and pediatric patients is usually assessed through ceruloplasmin-bound copper measurement, 24-hour urinary copper collection, and liver enzymes and function tests. 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 evaluated subjectively (i.e., based on patients' perspectives of symptoms), monthly after treatment initiation, and every 6 months to 12 months once stable. A neurologic assessment (with or without brain MRI) should be conducted at least annually, as should laboratory-based assessments (of non–ceruloplasmin-bound copper, 24-hour urinary copper excretion, and liver enzymes and function) to check for improvement; some patients may require more frequent testing, especially after treatment initiation. In pediatric patients, response to treatment should be assessed more frequently (e.g., every 3 months to 6 months) because the dosing is weight-based.

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 because patients cannot be left untreated. The main reason for treatment discontinuation would be inadequacy of treatment due to 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, a specialist does 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 to a specialist with experience treating Wilson disease — could be problematic for patients.

Drug Program Input

Key questions from the drug plans pertained to the reimbursement of trientine as a first-line treatment before DPA, use in children less than 5 years of age (given that Waymade-Trientine is approved only for patients ≥ 5 years), and restrictions on prescribers. The clinical experts advised that it is reasonable for trientine to be used before DPA in patients with a confirmed diagnosis of Wilson disease, and that there is no compelling reason why trientine could not be used in children less than 5 years of age; the main limitation is the lack of a pediatric dosage form. While the clinical experts believed that a specialist is required to diagnose Wilson disease and should be involved in the care of patients, prescribing for adult patients should not be limited to specialists. Due to the rarity of Wilson disease, there are few specialty clinics or specialists available with experience treating patients with Wilson disease. The experts also cautioned that it may be preferable not to place limitations on prescribers because these could lead to the undertreatment of adult patients who cannot access an experienced prescriber. Regarding the care of pediatric patients, the pediatric clinical expert advised that pediatric patients in Canada are managed only by pediatric specialists and subspecialists, not by other care providers.

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 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 the patients were treated. It appears that efficacy outcomes were based on the latest available follow-up evaluation within a 6-month to 48-month period. Data on discontinuations and discontinuations due to AEs were collected over a median 13.3-year period, but no range of time was reported. The results of the analysis were reported by the 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- 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. Given that the purpose of Study 17-VIN-0021 was to assess bioequivalence in healthy volunteers — not to assess 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, the baseline characteristics of the patients in the Weiss et al. (2013) study were reasonably similar to those of 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 with Wilson disease (the only age parameter reported in the study) was 17 years to 19 years. Although patients less than 18 years were included, no details on the number or ages of these pediatric patients were provided. At initial presentation, about half of patients (207 [51.1%]) had only hepatic symptoms; 92 patients (22.7%) had only neurologic symptoms; 52 patients (12.8%) had mixed presentations (i.e., both hepatic and neurologic symptoms); and 54 patients (13.3%) were asymptomatic. This distribution is similar to what would be 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 out of 38 trientine treatments [65.8%] versus 185 out of 295 DPA treatments [62.7%]) and for symptomatic patients (25 out of 27 trientine treatments [92.6%] versus 185 out of 204 DPA treatments [90.7%]); the scores were not statistically significantly different. Following second-line treatment, hepatic improvement scores were generally lower than with first-line treatment for all patients (i.e., 31 out of 103 trientine treatments [30.1%] and 12 out of 31 DPA treatments [38.7%]) and for symptomatic patients (31 out of 45 trientine treatments [68.9%] and 12 out of 16 DPA treatments [75.0%]). 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 out of 27 trientine treatments and 15 out of 204 DPA treatments). Stable hepatic disease after second-line therapy was reported in 10 out of 24 trientine treatments (22.2%) and 4 out of 16 DPA treatments (25%). 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 for all patients (i.e., 0 out of 38 trientine treatments [0%] versus 4 out of 295 DPA treatments [1.4%]) or for symptomatic patients (0 out of 27 trientine treatments (0%) versus 4 out of 204 DPA treatments (2.0%). While second-line trientine treatment was associated with hepatic worsening, there were no second-line DPA treatments associated with hepatic worsening (i.e., 4 out of 103 trientine treatments [3.9%] versus 0 out of 31 DPA treatments [0.0%] for all patients and 4 out of 45 trientine treatments [8.9%] versus 0 out of 16 DPA treatments [0.0%] for symptomatic patients). The differences between trientine and DPA treatments for hepatic worsening after either first- or second-line treatments were not statistically significantly different. Overall, there were 12 treatments with an outcome of liver transplantation (i.e., 3 trientine treatments [2.1%] and 9 DPA treatments [2.7%]).

Neurologic Impairment

In the Weiss et al. (2013) study, neurologic improvement scores for first-line treatment were comparable between trientine treatments (11 out of 38 [28.9%]) and DPA treatments (77 out of 295 [26.1%]) for all patients, but were numerically higher for DPA treatments (77 out of 114 [67.5%]) versus trientine treatments (11 out of 20 [55.0%]) in symptomatic patients; 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 out of 103 [25.2%]) but were numerically lower for DPA treatments (3 out of 31 [9.7%]). For symptomatic patients, neurologic improvement with second-line therapy after trientine treatments was numerically higher (26 out of 51 [51.0%]) than after DPA treatments (3 out 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 out of 20 trientine treatments (25.0%) and 31 out of 114 DPA treatments (27.2%) after first-line therapy and in 1 out of 51 trientine treatments (33.3%) and 9 out of 13 DPA treatments (69.2%) 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 out of 38 trientine treatments [10.5%] versus 6 out of 295 DPA treatments [2.0%]; P = 0.018) and for symptomatic patients (4 out of 20 trientine treatments [20.0%] and 6 out of 114 DPA treatments [5.3%]; P = 0.042). For second-line therapy, rates of neurologic worsening were numerically higher with trientine treatments compared to DPA treatments for all patients (8 out of 103 trientine treatments [7.8%] and 1 out of 31 DPA treatments [3.4%]) and symptomatic patients (8 out of 51 trientine treatments [15.7%] and 1 out of 13 DPA treatments [7.3%]). However, 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 out of 326 treatments [28.8%]) compared with trientine (10 out of 141 treatments [7.1%]). 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; the most common AEs (≥ 5% frequency in either group) that led to treatment discontinuation were arthralgia (29 out of 326 DPA treatments [8.9%] versus 4 out of 141 trientine treatments [2.8%]), increase in antinuclear antibodies (22 out of 326 DPA treatments [6.7%] versus 1 out of 141 trientine treatments [0.7%]), and albuminuria or proteinuria (20 DPA treatments [6.1%] versus an unreported number of trientine treatments). Rates of discontinuation for any reason were not statistically significantly different between the chelator treatments (P = 0.360), as reported in the publication.[13]

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. The latter circumstance may have introduced bias into the categorization of hepatic and neurologic outcomes and the identification of

symptomatic patients, given that 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 because an individual patient may have been counted more than once in the results. This would lead 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 minimal important differences (MIDs), 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 the 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 because children may not display the same clinical and laboratory hallmarks of the disease as adults.[14] No information on the dosage or administration schedules of trientine or DPA used in the study were reported; as a result, 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 of the efficacy outcomes identified in the review protocol, including outcomes of interest to patients, such as health-related quality of life (HRQoL) and adherence.

Conclusions

A retrospective cohort analysis of mainly adult patients with Wilson disease demonstrated that trientine has efficacy that is comparable to that of DPA for improving hepatic and neurologic outcomes when used as first-line therapy and when used as second-line therapy in patients who have failed or were intolerant to DPA. First-line treatment with trientine was associated with statistically significantly higher rates of neurologic worsening than treatment with DPA, but not when used as second-line treatment. More DPA treatments than trientine treatments were discontinued due to AEs, which was statistically significant. Due to the low quality of this study, there is considerable uncertainty about the relative estimates of efficacy and harms between trientine and DPA. Despite the limitations, this study comprises the largest body of evidence to date for the use of trientine in Wilson disease. Although the evidence is very limited, this must be placed in the context of the long market history of trientine worldwide and the experience gained in Canadian patients who received trientine through the SAP. The mechanism of action of trientine also represents a rational approach for the treatment of a disease caused by excess copper accumulation. Despite the many limitations associated with the evidence, Canadian patients with Wilson disease who fail on or cannot tolerate DPA currently have no alternative chelator option other than trientine. Wilson disease is associated with high morbidity and mortality in patients who are left untreated.

Introduction

Disease Background

Wilson disease (hepatolenticular degeneration) is a rare, heterogenous, inherited disease of copper metabolism that can present with hepatic, neurologic, or psychiatric involvement (or a combination of these). It can also be asymptomatic.[1,2] It is an autosomal recessive disorder associated with a mutation of the *ATP7B* gene, which encodes a metal-transporting P-type adenosine triphosphatase expressed primarily in hepatocytes that is involved in copper transport.[3] Reduced activity or absence of the ATP7B protein causes impaired hepatocellular excretion of copper into bile. This, in turn, leads to copper accumulation and liver injury, and eventually to the accumulation of copper elsewhere in the body, such as the brain, kidneys, and cornea.[3] An additional consequence of the loss of functional ATP7B protein is the inability to incorporate copper into ceruloplasmin. Ceruloplasmin is the major carrier protein for circulating copper in the blood, and accounts for 90% of the circulating copper in healthy individuals.[3]

Most patients with Wilson disease present between 5 years and 35 years of age, although patients are increasingly diagnosed in childhood or adolescence.[3,5,6,10] In children and younger adults, Wilson disease most often presents with liver disease. Neurologic manifestations tend to occur later in life due to the accumulation of copper in other organs after the liver has been saturated.[3-6] The clinical manifestations of Wilson disease vary widely. Liver presentations can range from asymptomatic enzyme elevations to fulminant hepatic failure (i.e., with severe coagulopathy, encephalopathy, acute Coombs-negative hemolysis, and rapidly progressive renal failure).[1] Other liver sequelae can include recurrent jaundice, acute hepatitis-like illness, autoimmune hepatitis, chronic liver disease, fatty liver, and hemolytic anemia due to the destruction of erythrocytes by the high serum concentration of non–ceruloplasmin-bound copper.[1] Neurologic symptoms include movement disorders (e.g., tremors, poor coordination, loss of fine motor control, chorea) or rigid dystonia (e.g., mask-like facies, rigidity, gait disturbance). Psychiatric presentations comprise depression, neurotic behaviour, personality disorder, affective changes, and intellectual deterioration.[1] Kayser-Fleisher rings — yellow-brown discolourations of the Descemet membrane in the cornea due to copper deposition — occur in 98% of patients with neurologic disease and in 80% of all cases of Wilson disease.[4]

The global prevalence of Wilson disease has been estimated to be 1 in 30,000 in most populations, with a carrier gene frequency ranging from 1 in 90 to 1 in 150 in the general population.[7,8] Each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.[1] First-degree relatives of a newly diagnosed patient must be screened for Wilson disease.[1,3] Lower prevalence rates for Wilson disease have been reported in North America versus other parts of the world.[15] Canadian-specific incidence and prevalence estimates are not available. However, in a retrospective chart review of 48 ambulatory patients with Wilson disease from Toronto Western Hospital, the median age at diagnosis was 17 years (range = 6 years to 63 years); 31.2% of patients presented with neurologic symptoms, 27.0% with hepatic symptoms, and 12.5% with mixed presentation. The remaining 29.2% of patients were asymptomatic, 50% of whom were diagnosed during family screening.[16]

Untreated Wilson disease is ultimately fatal. Most patients succumb to liver disease; a minority succumb to complications from progressive neurologic disease.[10] Mortality has not been assessed prospectively in Wilson disease; however, in general, survival prognosis

depends on the severity of liver and neurologic disease and on adherence to therapy (i.e., liver function can become normal after 1 year to 2 years of treatment in most patients who have no or compensated cirrhosis at presentation).[10] Acute liver failure often requires liver transplantation. In patients with Wilson disease who undergo orthotopic liver transplantation, early survival may be slightly reduced, but is considered normal for a transplant population.[10,17]

A diagnosis of Wilson disease is most often established through biochemical findings that — if observed in combination with low ceruloplasmin levels, the presence of Kayser-Fleisher rings, and clinical signs — are usually definitive for Wilson disease.[1,3] A diagnosis is confirmed through molecular genetic testing (i.e., single-gene testing, a multi-gene panel, or more comprehensive genomic testing, if required).[1,3] Biochemical findings associated with Wilson disease include low serum ceruloplasmin concentration, subnormal serum concentration of copper and of non-ceruloplasmin copper, high urinary copper, and increased hepatic copper concentration.[3] For many patients, a combination of tests reflecting disturbed copper metabolism may be needed to make a diagnosis. A diagnostic scoring system (Leipzig score) based on available tests has been developed.[18] The Leipzig scoring system considers typical clinical symptoms and signs of Wilson disease (i.e., the presence or absence of Kayser-Fleischer rings and Coombs-negative hemolytic anemia, severity of neurologic symptoms, and serum ceruloplasmin levels) as well as the results of other tests (i.e., copper levels in the liver and urine, mutation analysis).[18,19] Each factor is assigned a numerical score, with the total score ranging from 0 to 22.[18] A total Leipzig score of 4 or more establishes a diagnosis of Wilson disease; a score of 3 indicates that diagnosis is possible, but more tests are needed; and a score of 2 or less implies that diagnosis is very unlikely.[10,18] Another scoring system (Ferenci score) was proposed in 2001 to facilitate the diagnosis of Wilson disease in pediatric patients that takes into consideration the presence of Kayser-Fleischer rings, Coombs-negative hemolytic anemia, neuropsychiatric symptoms, urinary and liver copper, Rhodanine positive hepatocytes (only if quantitative copper measurement is unavailable), and the detection of disease-causing mutations. A Ferenci score of 0 to 1 is unlikely for Wilson disease; a score of 2 to 3 is probable; and a score of 4 or more is highly likely for the disease.[6]

Standards of Therapy

The treatment of Wilson disease is dependent on the presence of clinically relevant disease or laboratory or histological evidence of aggressive inflammatory hepatic or neurologic injury, and on whether the patient is identified before the onset of clinical symptoms.[3] Current treatment options for Wilson disease, such as chelation therapy or zinc salts, were first introduced into clinical practice more than 60 years ago with the goal of achieving a negative copper balance in the body.[3] Pharmacologic therapy for Wilson disease is lifelong, and although liver transplantation (which corrects the underlying hepatic defects) is usually curative, it is generally reserved for patients with acute liver failure or decompensated liver cirrhosis.[9]

The mainstays of treatment for Wilson disease are dietary copper restriction, chelation therapy, and zinc salts.[3] The first oral chelating drug for Wilson disease was DPA, which was introduced in 1956 and for which there is the most treatment experience worldwide.[3] The major action of DPA is to chelate copper through its free sulfhydryl group and to promote urinary excretion of the chelated copper.[3] DPA may also act by inducing metallothionein, an endogenous chelator of metals.[3] The usual maintenance adult dose of DPA is 750 mg/day to 1,500 mg/day. In children, DPA dosing is by body weight (i.e., 20 mg/kg/day), given in divided doses 2 to 3 times a day 1 hour before or 2 hours after meals or other medication (Table 2). Because DPA also interferes with pyridoxine, supplemental pyridoxine (25 mg/day

to 50 mg/day) should also be provided.[3] Trientine, a family of chelators with a polyamine-like structure chemically distinct from DPA, was first introduced in 1969 as an alternative to DPA.[3] Similar to DPA, trientine promotes the excretion of chelated copper by the kidneys.[3] Trientine has typically been used in patients who are intolerant of DPA or have clinical features indicating potential intolerance to DPA (e.g., renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency).[3] Typical doses range from 750 mg/day to 1,500 mg/day in adults and 20 mg/kg/day in children, spaced appropriately from meals or other medication, as with DPA. Zinc is also used to treat Wilson disease and was first introduced in the early 1960s.[3] Zinc acts by interfering with the absorption of copper from the gastrointestinal tract by inducing enterocyte metallothionein, which has greater affinity for copper than zinc; once bound, the copper is not absorbed, but eliminated in the fecal contents as enterocytes are shed in normal turnover.[3] Zinc is usually reserved for maintenance therapy post–de-coppering by chelation, although it may also be used in combination with chelation therapy.[3] Zinc has also been used as a first-line monotherapy option for patients who are asymptomatic or presymptomatic.[9] The usual dose is 150 mg/day elemental zinc in 3 divided doses for larger children and adults, 75 mg/day in 3 divided doses for children 6 years to 16 years of age weighing less than 50 kg, and 50 mg/day in 2 divided doses for children less than 6 years of age, all taken 30 minutes before meals.[9] Various zinc salts are available and while the actual salt used does not appear to affect the efficacy of zinc, it may influence tolerability.[9]

There are various limitations associated with currently available treatments for Wilson disease.[9] Although chelation therapy has been used for decades and is particularly beneficial in patients with hepatic symptoms, neurologic symptoms persist in about half of treated patients.[9] Moreover, approximately 10% of patients deteriorate neurologically during treatment; this deterioration is often irreversible.[9] An estimated 20% to 40% of patients with Wilson disease cannot be maintained on DPA due to intolerance, given that DPA is associated with many AEs, such as immediate hypersensitivity reactions, rash, nephrotic syndrome, myasthenia-like or lupus-like syndromes, and bone marrow toxicity, as well as worsening neurologic symptoms, which occur in approximately 10% to 50% of patients during the initial phase of treatment.[3,9] In general, AEs associated with DPA resolve once trientine is substituted and do not recur during prolonged treatment.[3,10] Although neurologic worsening with trientine has been reported, this happens less commonly than with DPA treatment.[3,10] Treatment regimens for Wilson disease are complex and burdensome for patients because they require multiple dosing regimens to be appropriately spaced over the course of each day with regard to food and concomitant medication.[9] Problems with adherence are observed in almost half of all patients with Wilson disease, which is a key concern given that treatment is lifelong.[9]

In describing the current treatment paradigm for Wilson disease, the clinical experts on the review team indicated that in Canada, chelation therapy is used as a first-line treatment, with or without zinc. Zinc may be added to address concerns about very excessive copper overload (to accelerate copper reductions) or to minimize the dose of chelator required (if there is intolerance or concern about worsening of neurologic symptoms). According to the clinical experts, most providers will initiate chelation therapy with DPA due to the historically limited access to trientine through the Health Canada SAP. The clinicians advised that when trientine has been accessed through the SAP, the brands used were Syprine and MAR-Trientine. Zinc is primarily used for maintenance therapy after successful chelation (typically after 1 year). It may also be used as initial monotherapy in people diagnosed through sibling screening, who often have limited copper overload, or as monotherapy in patients with a primary neurologic presentation, in whom chelators may worsen disease, sometimes irreversibly. Both chelation and zinc must be given chronically to avoid disease

progression. While both may improve symptoms over time, some symptoms, particularly neurologic symptoms, may show limited improvement, even with effective therapy. According to the clinical experts, the main goals of treatment are to prevent death, organ failure (liver and brain), disease progression, disability (neurologic, psychiatric), and liver transplantation; to reduce symptoms (hepatic, neurologic), improve quality of life, and minimize AEs; and to maintain independence and employment, thereby reducing caregiver burden.

Drug

Trientine is an oral 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.[11] Waymade-Trientine (trientine hydrochloride) is available as 250 mg oral capsules and is indicated for the treatment of patients with Wilson disease who are intolerant to penicillamine.[11] Waymade-Trientine is indicated only for the treatment of patients 5 years of age and older: based on the data submitted and reviewed by Health Canada, the safety and efficacy in patients less than 5 years of age has not been established.[11] The sponsor has requested reimbursement as per the Health Canada–approved indication. Waymade-Trientine has not previously been reviewed by CADTH; however, another trientine hydrochloride product (MAR-Trientine) was reviewed and received a draft recommendation to reimburse for the treatment of patients with Wilson disease who are intolerant to penicillamine if the following conditions are met:

- Patients must have previously tried and demonstrated intolerance to d-penicillamine.
- Reimbursement in pediatric patients should be limited to patients 5 years of age or older.
- For adult patients with Wilson disease, initiation, but not renewal, should be restricted to clinicians experienced in the management of Wilson disease.
- For pediatric patients with Wilson disease, both initiation and renewal should be restricted to clinicians experienced in the management of Wilson disease.
- A reduction in price.[20]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Group(s) and Information Gathered

CADTH received 1 patient group submission from the CLF for this drug. The CLF is dedicated to supporting education and research related to all forms of liver diseases and has invested in finding and understanding causes, preventive measures, and treatments for these. The group is committed to reducing the incidence and impact on Canadians at risk of or living with liver diseases. It reaches millions of people across Canada through educational programs, patient support programs, and awareness, fundraising, and outreach efforts. The CLF gathered information for this submission through an online questionnaire advertised on its website and social media platforms and provided directly to its Canadian patient, caregiver, and health care professional contacts. Overall, 8 patients and 5 caregivers responded. Additional input was collected from 2 health care professionals in addition to the direct call for patient input.

Disease Experience

Patients with Wilson disease said they felt that their condition had the greatest impact on their ability to exercise, work, travel, complete household activities, socialize, and fulfill family obligations. Caregivers reported that their ability to work and travel had been affected as well. One patient, who was also a student, noted that before chelation therapy, they had developed hand tremors that made writing difficult and caused them to withdraw socially. Another patient respondent even changed the copper pipes in their house to reduce the impact that they had on the copper levels in the tap water. Other patients described their experiences as follows:

Table 2: Key Characteristics of Therapies for Wilson Disease

Characteristic	Trientine	DPA	Zinc salts
Mechanism of action	Copper-chelating drug	Copper- and lead-chelating drug	Interferes with intestinal absorption of copper and induces enterocyte metallothionein
Indication[a]	For the treatment of patients with Wilson disease who are intolerant to penicillamine Indicated for patients ≥ 5 years of age only	For the treatment of Wilson disease, chronic lead poisoning, cystinuria, and patients with severe active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy	NA
Route of administration	Oral (available as 250 mg capsules)	Oral (available as 250 mg capsules)	Oral (different zinc salts are used: sulphate, acetate, or gluconate)
Recommended dose	500 mg/day to 2,000 mg/day on an empty stomach at least 1 hour before meals or 2 hours after meals and at least 1 hour apart from any other drug, food, or milk; given in divided doses 2 to 4 times a day	750 mg/day to 1,500 mg/day on an empty stomach at least 1 hour before meals or 2 hours after meals and at least 1 hour apart from any other drug, food, or milk; given in divided doses	150 mg elemental zinc/day (75 mg/day for children < 50 kg body weight); administered as 3 divided doses 30 minutes before meals
Serious adverse effects or safety issues	Worsening of neurologic or neurocognitive functioning that may be irreversible in patients with pre-existing neurologic or neuro-psychiatric impairment; iron deficiency anemia	Hypersensitivity and immune reactions, serious hematological and renal adverse reactions, hypogeusia	Gastritis (may be dependent on the zinc salt used), immunosuppressant effects, elevations in serum lipase or amylase
Other	Health Canada has not authorized an indication for children < 5 years because safety and efficacy have not been established in this population.	No age restriction. Due to interference with pyridoxine action, supplemental pyridoxine (25 mg/day to 50 mg/day) should be provided.	OTC therapy; if used in combination with chelators, dosing times must be spaced accordingly, which may be problematic for compliance with 3 times daily dosing.

DPA = d-penicillamine; EASL = European Association for the Study of the Liver; NA = not applicable; OTC = over the counter.

[a]Health Canada–approved indication.

Source: Waymade-Trientine product monograph[11]; Cuprimine product monograph[21]; Weiss et al. (2011)[22]; EASL Clinical Practice Guidelines: Wilson disease.[10]

"It has caused me to have stage 4 liver cirrhosis and some neurological symptoms. My life has been drastically altered since my diagnosis."

"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."

Experiences With Currently Available Treatments

The CLF submission identified emotional and psychological effects associated with living with and managing the illness, in addition to currently available treatments. In particular, those living with Wilson disease expressed feelings of constant stress and fear, psychiatric symptoms, and cases of bipolar disorder. Psychiatric symptoms, such as anxiety and depression, were described as negatively affecting patient and caregiver quality of life and as having the ability to "undermine the compliance needed to achieve disease regression."

Respondents listed the following side effects of current treatments as being completely to somewhat intolerable: fatigue, appetite loss, nausea, and pain. Fever, dizziness, forgetfulness, and stomach irritation were described as somewhat to very tolerable. Other symptoms that patients experienced with past treatments included lethargy, abnormal skin tightness, tingling hands, peripheral neuropathy, decreased platelets, constant muscle tension, and splenomegaly. Furthermore, respondents noted that these side effects were significant enough to reduce their quality of life and affect their activities of daily living. One caregiver described the issues with their patient's current treatment as follows: "Shelf life of her medication is only 10 days, and we have to order in advance as it has to made [sic] 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."

Improved Outcomes

Respondents felt that it is very important both to be able to access and have choice among treatments for Wilson disease and for patients and health care providers to make treatment choices based on known side effects. The survey results also emphasized the importance of the treatments' abilities to reduce short- and long-term side effects, improve overall quality of life, and allow for long- term stability. Respondents were interested in new treatments that would allow patients to take less medication, or to take it less frequently. One caregiver suggested that a single daily pill would be an improvement. Patients, caregivers, and health care professionals experience barriers and limitations in accessing treatment for Wilson disease. In this context, a patient stated that options should be more readily available to Canadians "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." Patients were aware of trials for new drugs taking place in other countries and were interested in seeing "treatment options be more available in Canada, along with clinical trials. And affordability and coverage with existing govt health coverage."

Experience With Drug Under Review

No survey respondents indicated having experience with Waymade-Trientine, but 2 patients and 2 caregivers reported experience with other trientine hydrochloride products; all had gained access through private insurance, albeit after various challenges throughout the process. Respondents reported that trientine hydrochloride was either effective or very effective at managing Wilson disease and said the side effects they experienced were mainly stomach irritation, fatigue, and minor pain.

In terms of challenges to gaining access to trientine hydrochloride, respondents mentioned obstacles with insurance companies, pharmacy channel gaps, issues with ongoing prescriptions, and medication contraindications. Patients who had previously gained access to the drug through the SAP indicated that obtaining insurance coverage had been a challenge, but generally felt that the process has since improved. A common theme among patients' experiences was having to wait months for approval, encountering challenges with insurance coverage, being denied, and having to pay out of pocket for the medication. (The latter poses a theoretical risk to some individuals of going untreated if costs are prohibitive.) A caregiver made the following remarks regarding the cost of the medication: "…some folks have financial hardship and they have to forgo treatment altogether. The price of trientine is ridiculous…. No one should have to decide between paying their rent/groceries and taking a lifesaving medication."

If they cannot access new medications, patients may have no choice in terms of their treatment options or associated side effects. One patient described being denied access to a trientine hydrochloride SAP. After discussing options with their hepatologist, they concluded: "…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."

One benefit of trientine hydrochloride that a couple of patients highlighted was that it does not require refrigeration. This makes it more convenient for storage and everyday use, and allows patients and caregivers to travel more easily. Both patients and caregivers expressed confidence that the drug would improve liver health, prevent further liver deterioration, and improve their quality of life.

Additional Information

Two health care providers who contributed to the patient input submission firmly advocated for better access to medications for their patients with Wilson disease. One said: "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." Another highlighted the fact that trientine hydrochloride has gained approval from Health Canada; thus, 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."

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of Wilson disease in adult and pediatric patients.

Unmet Needs

Not all patients will respond to, or tolerate, DPA or zinc. Canadian patients who require chelation and cannot take DPA due to toxicity or intolerance (at least 30% of patients) currently have no available chelation treatment options. Moreover, zinc is inadequate in about 30% of patients and is tolerated relatively poorly because it causes significant nausea and must be taken 3 times a day. The currently available treatments have limited efficacy in terms of reducing the likelihood of acute liver failure (i.e., fulminant Wilson disease presentation), 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 a specific drug formulation to meet pediatric needs (e.g., a liquid formulation).

Place in Therapy

Due to the rarity of Wilson disease, it is unlikely that randomized data comparing trientine to DPA will ever be available. The current use of trientine after DPA is mainly due to access issues. In the experts' opinion, if trientine were available as a first-line option, it would be preferred by many providers because it offers twice-daily dosing, few AEs, good tolerability, and solid efficacy. Other considerations that can affect its place in therapy are the relative costs of available therapies and the lack of a specific drug formulation to meet pediatric needs.

In a context where DPA and/or zinc must be tried before access to trientine is granted, the clinical experts advised that intolerance or lack of efficacy should be based on subjective inability to tolerate the medication (i.e., 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 because toxicity with DPA may be worse upon rechallenge. 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. This is particularly true with neurologic Wilson disease.

Patient Population

The diagnosis of Wilson disease can be challenging because no pathognomonic test is available. Multiple tests (e.g., biochemical blood tests, urine copper measurement, ophthalmologic examination, liver biopsy, and quantitative liver copper content) are required; these can be included in the Leipzig scoring system in adults or the Ferenci score for children to determine the likelihood of Wilson disease. Due to the rarity of the condition, it is poorly recognized by many providers. The unclear diagnostic pathway means many patients are diagnosed after irreversible neurologic and/or hepatic damage has occurred. Some patients present with acute liver failure and require transplantation. Simplification of the diagnostic pathway and better access to genetic testing in Canada would improve diagnosis and allow intervention before clinical presentation with advanced disease. Most patients are recognized when they present with symptomatic disease; although because of enhanced screening measures, patients increasingly present with liver blood test abnormalities. More patients are now found at presymptomatic stages (i.e., through sibling screening or due to increased awareness of Wilson disease and screening in the appropriate clinical context).

In terms of reducing overall body copper burden, it is expected that all patients with Wilson disease would respond to trientine. Both adult and pediatric patients with hepatic-prominent Wilson disease are likely to respond to chelation therapy, including trientine. Patients with

neurologic disease may worsen with the initiation of any chelator; some evidence and anecdotal reports suggest that neurologic worsening occurs more frequently with DPA than with trientine, although this idea is controversial and has not been evaluated rigorously. Patients with advanced and progressive neurologic and/or psychiatric disease would be considered least suitable for trientine treatment; however, trientine may still stabilize the disease and prevent further progression. Patients with acute liver failure often require immediate transplantation; trientine is unlikely to benefit those presenting with an acute Wilsonian crisis (i.e., acute liver failure and hemolytic anemia). Patients who have a confirmed diagnosis of Wilson disease but no symptoms should be treated; however, if the copper burden is not excessive, initial treatment with zinc is more appropriate than chelation therapy.

Assessing Response to Treatment

In clinical practice (and in the clinical trial setting), in both adult and pediatric patients, response to treatment is assessed through ceruloplasmin-bound copper measurements (calculated from serum copper and ceruloplasmin), 24-hour urinary copper collection, and liver enzymes and function tests. It is also important to assess neurologic and hepatic improvement following treatment (e.g., objective neurologic improvement, brain MRI, liver enzymes, and liver function) to monitor for ascites or jaundice. While some assessments are subjective, they can usually be supported by objective assessments. Treatment response should be evaluated subjectively (i.e., based on the patient's perspective of symptoms), monthly at initiation and every 6 months to 12 months once stable. Objective assessments, such as neurologic assessment with or without brain MRI, laboratory improvement (levels of non–ceruloplasmin-bound copper, 24-hour urinary copper excretion, liver enzymes and function), should be conducted at least annually, but may need to be done more frequently, especially at treatment initiation. In pediatric patients, response to treatment should be assessed at least every 6 months.

A clinically meaningful response to treatment would include: improved survival; prevention of liver transplantation; improved quality of life; stabilization of symptoms and organ function; normalization of liver tests; improvement in liver function (e.g., resolution of ascites or jaundice); neurologic and psychiatric symptom improvement; maintenance of independence; and improved adherence. There is no reason to expect that the magnitude of improvement would vary across physicians. However, neurologists may see less improvement than hepatologists because the liver responds better than the brain to treatment in Wilson disease.

Discontinuing Treatment

Treatment of Wilson disease is lifelong. In all cases, if a chelator treatment is stopped, an alternative chelator treatment must be started immediately because patients cannot be left untreated. The main reason for treatment discontinuation would be inadequacy of treatment due to either lack of efficacy or to tolerability issues. For example, a patient who receives chelation therapy for 1 to 2 years may transition to zinc monotherapy (which acts mainly by inhibiting the intestinal absorption of copper) for maintenance; however, if there is evidence of rising copper levels (e.g., non–ceruloplasmin-bound copper, 24-hour urinary copper excretion) and/or liver injury (e.g., liver enzyme elevation), the patient may need to return to chelation therapy for the long-term. Evidence of worsening neurologic function after chelator initiation should lead to prompt discontinuation of chelator therapy. Additionally, significant AEs known to be associated with DPA (e.g., rash, renal injury, neutropenia) should result in prompt discontinuation of DPA. While zinc can be used as a temporary therapy while waiting for approval of chelators, it is preferable to prevent delays in approval because even short periods of undertreatment can lead to significant disease progression.

Prescribing Conditions

Trientine can be safely prescribed in an outpatient clinic and/or specialty clinic setting. However, due to the rarity of Wilson disease, there are few specialty clinics. Once a clinical diagnosis of Wilson disease has been established, patients can be followed locally because not all will be able to access a specialty clinic for continuous care. Periodic consultation or oversight through a specialized Wilson disease program can supplement local care, but should not be a requirement for the prescription and/or approval of trientine. Close follow-up with patients and (in the case of pediatric patients) families is required to ensure adherence to therapy and to assess for sub-clinical disease or undertake genetic testing in siblings.

The clinical experts agreed that a specialist is required to diagnose Wilson disease and should be involved in patient care, but does not need to be the only prescriber of treatment. For pediatric patients, a specialist such as a pediatric hepatologist or metabolic disease specialist with experience in Wilson disease should be involved in the diagnosis, treatment, and monitoring of patients who would receive trientine. For adult patients, it may be preferable not to place limitations on prescribers because it may lead to the undertreatment of patients who struggle to find an experienced provider. With training, primary care providers should be able to initiate and monitor adult patients, although it is still preferable that a specialist be involved if possible. Hepatologists, gastroenterologists, and neurologists are the most relevant specialists, although general internal medicine specialists and pediatricians can play important roles, particularly in smaller communities and distant regions. Geneticists may be involved for diagnosis and possibly follow-up. Psychiatrists can provide ancillary support, but are rarely the primary specialists involved.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 3.

Clinical Evidence

The clinical evidence included in the review of Waymade-Trientine is presented in the following section. The systematic review includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada. No additional studies that met the inclusion criteria (as per the a priori protocol) for the systematic review were identified in the literature. No indirect evidence was submitted by the sponsor or identified from the literature. Further, no sponsor-submitted, long-term extension studies or additional relevant studies were considered to address important gaps in the evidence; therefore, no additional evidence was included in this review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of trientine hydrochloride 250 mg oral capsules for the treatment of Wilson disease in patients who are intolerant to penicillamine.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada as well as those meeting the selection criteria presented in Table 4. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[23]

This report makes use of a literature search developed for a previous CADTH report.[24] For the previous report, published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid and Embase (1974–) through Ovid. All Ovid

Table 3: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert responses
Clinicians may wish to access trientine before DPA due to its better tolerability profile. Is it reasonable to allow use as first-line treatment, and if so, what criteria should apply?	Yes, it is reasonable for trientine to be used before DPA in patients with a confirmed diagnosis of Wilson disease because it has a better tolerability profile and is associated with fewer AEs. The use of trientine after DPA is not evidence-based and is largely due to access issues.
Trientine is approved for use in only 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?	Yes, it should be allowed. There is no compelling reason not to use trientine in a child < 5 years of age; the main limitation is that it is not available in a dosage form amenable to dosing in children (e.g., liquid formulation, given that the capsules should not be opened or chewed).[11] It is expected that use in children < 5 years of age would be infrequent.
The product monograph states that trientine should be initiated only 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?	Please refer to the Prescribing Conditions section of this report for more detailed information in response to this question. A specialist is required to diagnose Wilson disease and should be involved in the care of patients, but should not be the only prescriber of treatment. Due to the rarity of Wilson disease, there are few specialty clinics available. Once a patient has been diagnosed, they can be followed locally; however, a specialist should provide oversight and ongoing support, as needed.
Should prescribing be restricted to certain specialists (e.g., gastroenterologists, hepatologists, internal medicine), or can it be done by all practitioners?	Please refer to the Prescribing Conditions section of this report for more detailed information in response to this question. Prescribing should not be restricted to specialists. For adult patients, it may be preferable not to place limitations on prescribers because it may lead to undertreatment of patients who are not able to access an experienced provider.

AE = adverse event; DPA = d-penicillamine.

searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were trientine and Wilson disease. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

Table 4: Inclusion criteria for the systematic review

Criteria	Description
Population	Patients ≥ 5 years of age with Wilson disease who are intolerant to penicillamine. Subgroups: • Age (< 18 years vs. ≥ 18 years) • Disease status at diagnosis (i.e., asymptomatic, hepatic, neurologic, or combined hepatic and neurologic presentation) • Use as first-line vs. second-line therapy
Intervention	Trientine hydrochloride 500 mg/day to a maximum of 2,000 mg/day orally on an empty stomach in divided doses 2 to 4 times a day.
Comparators	• MAR-Trientine (trientine hydrochloride) • DPA • Zinc • No treatment
Outcomes	**Efficacy outcomes:** • Survival • HRQoL using validated scales[a] • Hepatic impairment (e.g., hepatic dysfunction or decompensation, histologic changes, hepatocellular carcinoma, liver transplantation) • Neurologic impairment (e.g., dysarthria, ataxia, dystonia) and neurologic symptoms measured using validated scales • Psychiatric manifestations • Copper levels (i.e., free serum, urinary) • Adherence[a] • Health care resource utilization **Harms outcomes:** AEs, SAEs, WDAEs, mortality, AEs of special interest (e.g., rash, nephrotoxicity, polyneuropathy, pancytopenia, polymyositis, optic neuritis, iron deficiency anemia)
Study designs	Published and unpublished RCTs

AE = adverse event; DPA = d-penicillamine; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

[a]These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The initial search was completed on May 17, 2021. For the current report, database searches were rerun on September 13, 2021 to capture any articles published since the initial search date. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on December 15, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the CADTH checklist, Grey Matters: a *practical tool for searching health-related grey literature*.[25] Included in this search were the websites of regulatory agencies (the US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the drug sponsor was contacted for information regarding unpublished studies.

A focused literature search for network meta-analyses dealing with Wilson disease was run in MEDLINE All (1946–) on May 14, 2021. No limits were applied to the search.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

No studies were identified from the literature for inclusion in the systematic review (Figure 1).The only included studies are the pivotal studies provided in the sponsor's submission to CADTH and Health Canada, which are summarized in Table 5.

Description of Studies

Two pivotal studies were submitted by the sponsor and included in the systematic review. The Weiss et al. (2013) study was a retrospective cohort analysis of 405 patients with Wilson disease who were treated with trientine or DPA. Study 17-VIN-0021 was an open-label, 2-period, 2-sequence, 2-treatment, crossover, single-dose, fasting, bioequivalence study of trientine hydrochloride 250 mg capsules USP (test) compared to Syprine (trientine hydrochloride) 250 mg capsules (reference) in healthy volunteers. Because 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.

The objective of the Weiss et al. (2013) study was to evaluate the efficacy and safety of DPA compared to trientine therapy based on hepatic and neurologic outcomes and AEs that led to treatment discontinuation. Data on the initial presentation of patients and the development of clinical and laboratory parameters under treatment with DPA or trientine were retrospectively collected from the records of 380 patients who were examined at an unspecified number of tertiary care centres in cities in Germany (Heidelberg, Dresden, and Dusseldorf) and Austria (Vienna, Graz, and Linz) and from 25 patients who were identified from the EUROWILSON patient registry who had been treated with trientine monotherapy (i.e., a total of 405 patients). Patients with a stable disease course were seen at the tertiary centres approximately once

per year, although patients were followed more closely if there was a change in medical therapy (e.g., at 3 months, 6 months, or 12 months after initiation of the change). Patients were included only if the duration of treatment was 6 months or more. The duration of follow-up was not clearly defined; however, it appears that efficacy outcomes were based on the latest follow-up evaluation within a 6-month to 48-month follow-up period, while harms outcomes were based on a median follow-up of 13.3 years, although no range or time frame for collection of these data was specified.

Based on the symptoms present at the time of diagnosis, patients were categorized into the following subgroups: asymptomatic, hepatic, neurologic, or mixed presentation (i.e., having both hepatic and neurologic symptoms). Hepatic and neurologic outcomes were also categorized according to first- or second-line use of trientine or DPA. The results of the analysis were not reported by patient, but rather by the number of chelator monotherapies received. There were a total of 467 chelator-based treatments (i.e., 326 DPA monotherapy treatments and 141 trientine monotherapy treatments). Because there were 405 patients included in the analysis, an individual patient could have received both DPA and trientine in

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

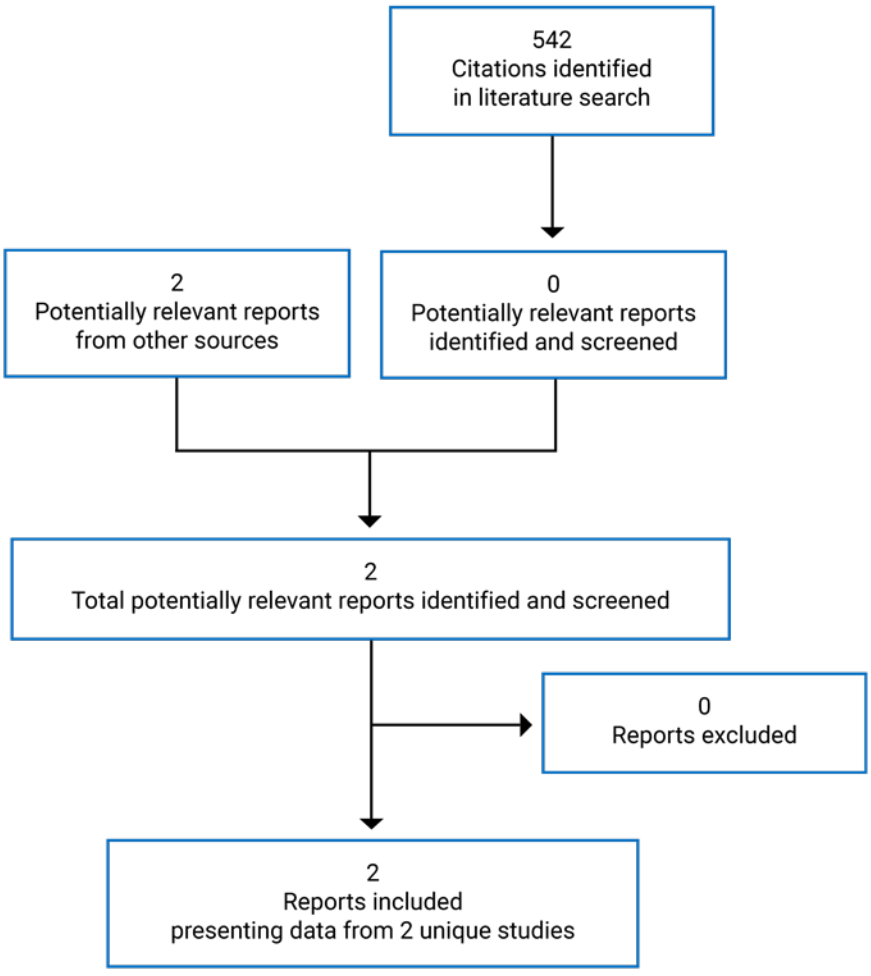


Table 5: Details of Included Studies

Characteristic	Weiss 2013 Study	Study 17-VIN-0021[c]
Designs and populations		
Study design	Retrospective cohort study	Open-label, randomized, 2-period, 2-sequence, crossover, single-dose, oral bioequivalence study
Locations	Germany, Austria, EUROWILSON Registry[a]	India
Patient enrolment dates	NR	August 16, 2017 to August 31, 2017
N	405 (non-randomized)	44 (enrolled); 38 (analyzed)
Inclusion criteria	Diagnosis of Wilson disease and Leipzig score > 4, *ATP7B* mutational status	Healthy male volunteers 18 years to 45 years of age, preferably with a BMI of 18.0 kg/m^2 to 30.0 kg/m^2; minimum weight 45 kg, negative drug and alcohol screen
Exclusion criteria	Leipzig score < 4, patients receiving only zinc salts or combination of zinc salts and chelator over the study treatment period, follow-up < 6 months	• Hypersensitivity to trientine or related drug class • History of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, urogenital, neurologic, or psychiatric disease or disorder • Use of any treatment that could bring about the induction or inhibition of the hepatic microsomal enzyme system within 1 month before dosing • History or presence of any of the following: significant alcoholism or drug abuse in the past 1 year; significant smoking, asthma, urticaria, or other significant allergic reactions; significant gastric and/or duodenal ulceration; significant thyroid disease, adrenal dysfunction, organic intracranial lesion; cancer or basal or squamous cell carcinoma
Drugs		
Intervention	Trientine monotherapy (dose NR)	Trientine hydrochloride 250 mg capsules (manufactured by Apothecon Pharmaceuticals Pvt. Ltd.), single-dose 250 mg PO (test)
Comparator(s)	DPA monotherapy (dose NR)	Syprine (trientine hydrochloride) 250 mg capsules (manufactured by Pharmaceutics International Inc., US and distributed by Valeant Pharmaceuticals, US), single-dose 250 mg PO (reference)
Duration		
Phase		
• Run in	NA	NA
• Open-label period	NA	Single dose of each treatment with 11-day washout between periods
• Follow-up	48 months[b]	NA

Characteristic	Weiss 2013 Study	Study 17-VIN-0021[c]
Outcomes		
Primary end point	Hepatic and neurologic outcomes (i.e., scored as unchanged, improved to normal, improved but not normal, deteriorated, or asymptomatic)	AUC0-T AUC0-∞ C_{max}
Secondary and exploratory end points	NA	NA
Notes		
Publications	Weiss et al. (2013)[13]	None

AUC0-t = area under the concentration-time curve to last quantifiable concentration; AUC0-∞ = area under the concentration-time curve to infinity; BMI = body mass index; C_{max} = maximum measured concentration; DPA = d-penicillamine; NA = not applicable; NR = not reported; PO = oral.

Note: Two additional reports were included: the sponsor's submission[27]; the Health Canada Reviewer Report.

[a]Among the 405 total patients, 380 patients were enrolled from tertiary care centres in Austria and Germany, and 25 were included from the EUROWILSON Registry, which enrols patients from Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, India, Italy, Netherlands, Norway, Pakistan, Poland, Portugal, Romania, Serbia, Spain, Switzerland, Turkey, and the UK.[26]

[b]The duration of follow-up was not clearly defined; however, it appears that efficacy outcomes were based on the latest follow-up evaluation within a 6-month to 48-month follow-up period and harms outcomes were based on a median follow-up of 13.3 years (no range was reported).

[c]Because the purpose of Study 17-VIN-0021 was to assess bioequivalence in healthy volunteers, not the efficacy and safety of trientine in patients with Wilson disease, this study was not reviewed in detail in this report.

Source: Weiss et al. (2013)[13]; Study 17-VIN-0021 Clinical Study Report.[28]

separate monotherapy regimens. No information was reported on the efficacy and safety of switching between DPA and trientine chelator therapies in individual patients. This study was supported by a grant from the Dietmar Hoppf Foundation, a Young Investigator Grant from the Medical Faculty of the University of Heidelberg, and an unrestricted educational grant from the German Wilson disease patient organization, Morbus Wilson e.V. EuroWilson was a Coordination Action funded by the 6th European Union Programme Framework.

Populations

Inclusion and Exclusion Criteria

There were no inclusion criteria specified in the Weiss et al. (2013) study. Rather, patients from an unspecified number of tertiary care centres in Germany and Austria and patients identified from the EUROWILSON registry were included. The diagnosis of Wilson disease was based on the Leipzig score; patients who had a score greater than or equal to 4 were included. Patients who received only zinc salts or a combination of zinc and a chelator therapy were excluded from the analysis. Patients who had a follow-up of less than 6 months were also excluded. Therefore, patients with acute liver failure who underwent liver transplantation soon after diagnosis with Wilson disease were excluded.

Baseline Characteristics

In the Weiss et al. (2013) study, baseline characteristics were recorded at the time of treatment initiation or change in the chelator- based treatment regimen. The presence of Kayser-Fleischer rings was established by slit-lamp examination, and a diagnosis of cirrhosis was based on histology or on the presence of clinical signs of portal hypertension.

Baseline demographic and disease characteristics by chelator treatment were reported by the number of chelator treatments only, as detailed in Figure 2. Of the 326 DPA monotherapies, most treatments (294 [90.2%]) were first-line therapies, whereas of the 141 trientine

monotherapies, the majority of treatments (105 [74.5%]) were second-line. The median age at diagnosis was 17.5 years for DPA treatment compared with 19.5 years for trientine treatment. Notable differences (i.e., ≥ 5%) between DPA and trientine treatments were the proportions of treatments categorized at initial presentation as neurologic (72 [22.1%] versus 39 [27.7%]) or asymptomatic (52 [16%] versus 13 [9.2%]) for DPA and trientine, respectively. All other baseline characteristics appeared to be similar between the treatments.

Baseline characteristics by number of patients were available only collectively for the whole study cohort (not by treatment). Of the 405 included patients, 238 (58.8%) were female and 167 (41.2%) were male. At initial presentation, 207 of all patients (51.1%) had only hepatic symptoms, 92 (22.7%) had only neurologic symptoms, 52 (12.8%) had hepatic and neurologic symptoms, and 54 (13.3%) were asymptomatic. There were 21 (5.2%) patients who presented with fulminant liver disease (acute liver failure); 120 out of 399 patients (30.1%) had cirrhosis at diagnosis. Overall, 64 (15.8%) of all patients were diagnosed by family screening, and 205 out of 379 (54.1%) patients had Kayser-Fleischer rings present at the time of diagnosis.

Interventions

In the Weiss et al. (2013) study, the rationale for selecting a chelator therapy (i.e., DPA or trientine) for a patient was not stated because the data were collected retrospectively. According to the researchers, patients generally started chelation therapy when symptomatic. Further, no information on the dosage or treatment regimens used for either trientine or DPA

Figure 2: Summary of Baseline Characteristics by Number of Chelator Treatments (Weiss et al. [2013] Study)

	DPA (n = 326 analyzed)	Trientine (n = 141 analyzed)	*P* value
Sex: male:female	131:195	53:88	.589
Initial presentation			
Hepatic	167/326 (51.2%)	69/141 (48.9%)	.134
Neurologic	72/326 (22.1%)	39/141 (27.7%)	
Hepatic and neurologic	35/326 (10.7%)	20/141 (14.2%)	
Asymptomatic	52/326 (16%)	13/141 (9.2%)	
ATP7B genotype: H1069Q/H1069Q	64/326 (19.6%)	26/141 (18.4%)	.764
Median age at diagnosis, y	17.51 (0.74–60.05)	19.51 (1.23–55.06)	.056
Kayser–Fleischer rings present	170/300 (56.7%)	83/135 (61.5%)	.346
Cirrhosis	92/300 (30.7%)	47/140 (33.6%)	.300
Treatment used as first-line treatment	294/326 (90.2%)	36/141 (25.5%)	< .001
Body mass index[a]	22.5 (14.8–32.4)	22.7 (17.7–27.7)	.64
AST level, U/L[b]	32 (4–2106)	34.62 (13–179)	.449
ALT level, U/L[b]	40 (4–3743)	41 (10–505)	.815
gGT level, U/L[b]	52 (6–708)	56 (12–1021)	.452
Bilirubin level, mg/dL[c]	0.8 (0.2–47)	0.7 (0.1–16.2)	.703
INR[d]	1.02 (1–3)	1.06 (1–3)	.442
Albumin level, g/L[e]	43 (23–55)	42.6 (28–58)	.571
MELD score[d]	7.5 (6.4–35.3)	7.5 (6.4–17.1)	.963
Serum copper level, μmol/L[c]	7 (1–145)	6.9 (1–24)	.652
Ceruloplasmin level, g/L[b]	0.095 (0–0.94)	0.10 (0.2–0.38)	.765

NOTE. *P* values for comparison between treatments were calculated by the chi-square Pearson or the Mann–Whitney *U* test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; gGT, γ-glutamyltransferase; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]Data available for DPA, n = 37; trientine, n = 10.
[b]Data available for DPA, n = 184; trientine, n = 49.
[c]Data available for DPA, n = 161; trientine, n = 46.
[d]Data available for DPA, n = 71; trientine, n = 31.
[e]Data available for DPA, n = 134; trientine, n = 47.

DPA = d-penicillamine.

Source: Reprinted from Clinical Gastroenterology and Hepatology, Vol 11, Issue 8, Weiss KH, Thurik F, Gotthardt DN, et al., Efficacy and safety of oral chelators in treatment of patients with Wilson disease, pp1028 to 1035.E2, 2013 with permission from the American Gastroenterological Association.[13]

was provided. The duration of treatment was also not clearly defined, nor was the time frame of the study or the calendar years over which the patients were treated.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 6.

In the Weiss et al. (2013) study, hepatic and neurologic outcomes were assessed at 6 months, 12 months, 24 months, 36 months, and 48 months after initiation of the patient's current treatment regimen, and the reported outcomes were based on the latest available follow-up evaluation within the 6-month to 48-month follow-up period. No rationale was provided for the choice of the 48-month follow-up period.

Hepatic outcome measures were derived from patient records and were based on clinical symptoms, course of liver enzymes, and results of liver function tests, as assessed by the researchers. Patients with either clinical or biochemical signs of liver disease were considered symptomatic. Neurologic outcomes were also derived from patient records, and were based on the course of neurologic disease as evaluated by the patient's physician. Both hepatic and neurologic outcomes were categorized by the researchers as 1 of: unchanged, improved to normal, improved but not normal, deteriorated, or asymptomatic over duration. For hepatic symptoms, the improved-to-normal category implied normalized liver enzymes and liver function tests.

Harms were assessed as the number of discontinued treatments. Reasons for stopping or changing therapy were categorized by the researchers as: AEs, orthotopic liver transplantation, pregnancy, patient request, and other (not specified). The time period for collection of the harms outcomes was not stated; it was reported only that the median follow-up for the analysis of reasons for discontinuation of treatment and AEs was 13.3 years (no range was specified).

Statistical Analysis

Power Calculation

In the Weiss et al. (2013) study, no sample size or power calculation was reported. Of note, the efficacy outcomes reported in the study were not identified as either primary or secondary outcomes.

Statistical Tests

There was no statistical analysis plan available for the Weiss et al. (2013) study. The efficacy outcomes reported were improvement or worsening of hepatic or neurologic outcomes. These were categorized as previously described and counted as number of chelator monotherapy treatments. Comparisons of hepatic and neurologic outcomes between DPA and trientine monotherapy treatments were conducted using the 2-tailed Fischer exact test.

Table 6: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Weiss 2013	Study 17-VIN-0021
Hepatic impairment	Not specified as primary or secondary	NA
Neurologic impairment	Not specified as primary or secondary	NA

NA = not applicable.

A P value of less than 0.05 was considered statistically significant. No further information on the statistical analyses of the efficacy outcomes was reported. No data imputation methods were mentioned, and no statistical adjustments were made for multiple comparisons to control the type I error rate.

Regarding harms outcomes, events leading to a change or discontinuation of a chelator monotherapy treatment were categorized by the authors and analyzed using Kaplan–Meier estimation. P values were derived using the log-rank test (Mantel-Cox test). A P value of less than 0.05 was considered statistically significant. No further information was reported on the statistical analyses of discontinuation, harms outcomes, or Kaplan–Meier analysis.

Subgroup Analyses

There were no pre-specified subgroups in the Weiss et al. (2013) study. Nonetheless, efficacy outcomes of hepatic or neurologic worsening or improvement were reported for all patients and for a subpopulation of patients categorized as symptomatic and according to first-line or second-line treatment with trientine or DPA. There did not appear to be an evaluation of the comparability of the apparent subgroups between the chelator monotherapies, and there were no statistical adjustments made for multiple comparisons to control for type I error.

Analysis Populations

In the Weiss et al. (2013) study, the analysis population comprised the number of chelator monotherapy treatments (N = 467). The number of patients contributing to the analysis population included 380 patients examined at an unspecified number of tertiary care centres in Germany and Austria and 25 patients identified from the EUROWILSON registry who were treated with trientine monotherapy.

Results

Treatment Disposition

For the Weiss et al. (2013) study, the disposition data pertain to the number of chelator monotherapy treatments (not the number of individual patients), as detailed in Figure 3. Overall, 142 DPA treatments (43.6%) were discontinued compared with 36 trientine treatments (25.5%) over the study duration; the specific time period for this is unknown. The main reasons for discontinuation of DPA treatment were AEs (in 94 treatments [28.8%]) followed by other (in 23 treatments [7.1%]), which was not defined. For trientine, the main reason for treatment discontinuation was other (in 18 treatments [12.8%]) followed by AEs (in 10 treatments [7.1%]). There were 12 treatments discontinued due to liver transplantation after hepatic failure (i.e., 9 DPA treatments [2.8%] and 3 trientine treatments [2.1%]). There

Table 7: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Sensitivity analyses
Weiss et al. (2013)			
Hepatic and neurologic outcomes	Fisher exact test (2-tailed)	NA	NA
Events leading to treatment discontinuation	Kaplan–Meier estimation Log-rank test (Mantel-Cox test)	NA	NA

NA = not applicable.

were 4 DPA treatments (1.2%) that were discontinued due to pregnancy; no trientine treatments were discontinued for this reason.

Exposure to Study Treatments

In the Weiss et al. (2013) study, efficacy outcomes were assessed from patient records for up to 48 months after initiation or change in chelator monotherapy. For the analysis of treatment discontinuations, all that was provided was the statement that the median follow-up time for the Kaplan–Meier estimation was 13.3 years; there was no other explanation of the methodology used. No additional information was provided regarding exposure to either DPA or trientine treatment.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here. There were no data reported in the included studies for the following outcomes of interest as per the protocol for this systematic review: HRQoL, psychiatric manifestations, copper levels, adherence, or health care resource utilization.

Hepatic Impairment

Results of the detailed scoring of hepatic outcomes for all trientine and DPA chelator treatments included in the Weiss et al. (2013) study are provided in Figure 4. No statistical comparisons were conducted for these outcomes. Similar proportions of trientine and DPA monotherapy treatments were scored as "unchanged" (12 trientine treatments [8.5%] versus

Figure 3: Treatment Disposition

Reasons for discontinuation	Number of discontinued treatments: DPA (n = 326)	Number of discontinued treatments: Trientine (n = 141)	*P* value
OLT	9	3	.360
Adverse events	94	10	.039
Pregnancy	4	0	.402
Patient request	12	5	.390
Other	23	18	< .001
Total (any reason)	142	36	.360

NOTE. *P* values for comparison between treatments were established using the Mantel–Cox test.
OLT, orthotopic liver transplantation.

DPA = d-penicillamine.

Source: Reprinted from Clinical Gastroenterology and Hepatology, Vol 11, Issue 8, Weiss KH, Thurik F, Gotthardt DN, et al., Efficacy and safety of oral chelators in treatment of patients with Wilson disease, pp1028 to 1035.E2, 2013 with permission from the American Gastroenterological Association.[13]

19 DPA treatments [5.8%]) and "improved but not normal" (27 trientine treatments [19.1%] versus 58 DPA treatments [17.8%]). More than double the number of DPA treatments (139 [42.6%]) were scored as "improved to normal" versus trientine treatments (29 [20.6%]). Further, a numerically larger proportion of trientine treatments (69 [48.9%]) were scored as "asymptomatic over the study duration" compared with DPA treatments (106 [32.5%]). Only a small proportion of both trientine treatments (4 [2.8%]) and DPA treatments (4 [1.2%]) were scored as "deteriorated."

Rates of hepatic improvement and worsening for trientine and DPA treatments by line of treatment for all patients or symptomatic patients, as reported by the researchers, are provided in Figure 5. Hepatic improvement scores after first-line treatment were comparable for all patients (25 out of 38 trientine treatments [65.8%] versus 185 out of 295 DPA treatments [62.7%]) and for symptomatic patients (25 out of 27 trientine treatments [92.6%] versus 185 out of 204 DPA treatments [90.7%]); these scores were not statistically significantly different (Figure 5). Following second-line treatment, hepatic improvement scores were generally lower than with first-line treatment (i.e., 31 out of 103 trientine treatments [30.1%] and 12 out of 31 DPA treatments [38.7%] for all patients, and 31 out of 45 trientine treatments [68.9%] and 12 out of 16 DPA treatments [75.0%] for symptomatic patients). There were also no statistically significant differences between treatments. For

Figure 4: Detailed Scoring of Hepatic or Neurologic Outcomes by Number of Chelator Treatments (Weiss et al. [2013])

	DPA (n = 326)	Trientine (n = 141)
Unchanged		
Neurologic	40/326 (12.3%)	22/141 (15.6%)
Hepatic	19/326 (5.8%)	12/141 (8.5%)
Improved but not normal		
Neurologic	58/326 (17.9%)	33/141 (23.4%)
Hepatic	58/326 (17.8%)	27/141 (19.1%)
Improved to normal		
Neurologic	22/326 (6.7%)	4/141 (2.8%)
Hepatic	139/326 (42.6%)	29/141 (20.6%)
Asymptomatic over duration		
Neurologic	199/326 (61%)	70/141 (49.6%)
Hepatic	106/326 (32.5%)	69/141 (48.9%)
Deteriorated		
Neurologic	7/326 (2.1%)	12/141 (8.5%)
Hepatic	4/326 (1.2%)	4/141 (2.8%)

NOTE. All 515 treatment outcomes as scored at the end of the follow-up period of up to 48 months.

DPA = d-penicillamine.

Source: Reprinted from Clinical Gastroenterology and Hepatology, Vol 11, Issue 8, Weiss KH, Thurik F, Gotthardt DN, et al., Efficacy and safety of oral chelators in treatment of patients with Wilson disease, pp1028 to 1035.E2, 2013 with permission from the American Gastroenterological Association.[13]

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 out of 27 trientine treatments and 15 out of 204 DPA treatments). Stable hepatic disease after second-line therapy was reported in 10 out of 24 (22.2%) trientine treatments and 4 out of 16 (25%) 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 out of 38 trientine treatments [0]% versus 4 out of 295 DPA treatments [1.4%] for all patients and 0 out of 27 trientine treatments [0%] versus 4 out of 204 DPA treatments [2.0%] for symptomatic patients) (Figure 5). While second-line trientine treatment was associated with hepatic worsening, no second-line DPA treatments were associated with hepatic worsening (i.e., 4 out of 103 trientine treatments [3.9%] versus 0 out of 31 DPA treatments [0.0%] for all patients, and 4 out of 45 trientine treatments [8.9%] versus 0 out of 16 DPA treatments [0.0%] 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 trientine treatments [2.1%] and 9 DPA treatments [2.7%]).

Neurologic Impairment

Results of the detailed scoring of neurologic outcomes for all trientine and DPA chelator treatments included in the Weiss et al. (2013) study are provided in Figure 4. No statistical comparisons were conducted for these comparisons. Most treatments for either trientine (70 out of 141 [49.6%]) or DPA (199 out of 326 [61.0%]) were scored as asymptomatic over the duration. There were numerically more DPA treatments (22 out of 326 [6.7%]) than trientine treatments (4 out of 141 [2.8%]) scored as improved to normal. The proportions of trientine and DPA monotherapy treatments that were scored as unchanged were 22 out of 141 (15.6%) and 40 out of 326 (12.3%), whereas those scored as improved but not normal were 33 out of 141 (23.4%) and 58 out of 326 (17.9%), respectively. There were numerically more treatments

Figure 5: Rate of Hepatic or Neurologic Improvement and Worsening by Number of Chelator Treatments (Weiss et al. [2013])

	First-line treatments			Second-line treatments		
	DPA	Trientine	*P* value	DPA	Trientine	*P* value
Hepatic improvement						
All	185/295 (62.7%)	25/38 (65.8%)	.859	12/31 (38.7%)	31/103 (30.1%)	.386
Symptomatic	185/204 (90.7%)	25/27 (92.6%)	1	12/16 (75%)	31/45 (68.9%)	.757
Hepatic worsening						
All	4/295 (1.4%)	0/38	1	0/31	4/103 (3.9%)	.573
Symptomatic	4/204 (2%)	0/27	1	0/16	4/45 (8.9%)	.565
Neurologic improvement						
All	77/295 (26.1%)	11/38 (28.9%)	.699	3/31 (9.7%)	26/103 (25.2%)	.082
Symptomatic	77/114 (67.5%)	11/20 (55%)	.312	3/13 (23.1%)	26/51 (51%)	.118
Neurologic worsening						
All	6/295 (2%)	4/38 (10.5%)	.018	1/31 (3.4%)	8/103 (7.8%)	.684
Symptomatic	6/114 (5.3%)	4/20 (20%)	.042	1/13 (7.3%)	8/51 (15.7%)	.672

NOTE. *P* values were established using the 2-tailed Fisher test.

DPA = d-penicillamine.

Source: Reprinted from Clinical Gastroenterology and Hepatology, Vol 11, Issue 8, Weiss KH, Thurik F, Gotthardt DN, et al., Efficacy and safety of oral chelators in treatment of patients with Wilson disease, pp1028 to 1035.E2, 2013 with permission from the American Gastroenterological Association.[13]

scored as deteriorated with trientine (12 out of 141 [8.5%]) compared with DPA (7 out of 326 [2.1%]).

Rates of neurologic improvement and worsening for trientine and DPA by line of treatment and for all patients or symptomatic patients are provided in the bottom half of Figure 5. Neurologic improvement scores for first-line treatment were comparable between trientine treatments (11 out of 38 [28.9%]) and DPA treatments (77 out of 295 [26.1%]) for all patients, but were numerically higher for DPA treatments (77 out of 114 [67.5%]) versus trientine treatments (11 out of 20 [55.0%]) in symptomatic patients; however, the differences were not statistically significant (Figure 5). Following second-line therapy for all patients, neurologic improvement rates were comparable to those after first-line therapy for trientine treatments (26 out of 103 [25.2%]), but were numerically lower for DPA treatments (3 out of 31 [9.7%]). For symptomatic patients, neurologic improvement with second-line therapy after trientine treatments (26 out of 51 [51.0%]) was numerically higher than after DPA treatments (3 out of 13 [23.1%]). Nonetheless, all comparisons between trientine treatments and DPA treatments for all patients and for 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 out of 20 trientine treatments (25.0%) and 31 out of 114 DPA treatments (27.2%) after first-line therapy and in 1 out of 51 trientine treatments (33.3%) and 9 out of 13 DPA treatments (69.2%) 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 out of 38 [10.5%] versus 6 out of 295 [2.0%], respectively; P = 0.018) and for symptomatic patients (4 out of 20 [20.0%] and 6 out of 114 [5.3%], respectively; P = 0.042) (Figure 5). For second-line therapy, rates of neurologic worsening were numerically higher with trientine treatments compared to DPA treatments for all patients (8 out of 103 [7.8%] and 1 out of 31 [3.4%], respectively) and symptomatic patients (8 out of 51 [15.7%] and 1 out of 13 [7.3%], respectively); however, the differences were not statistically significant.

Harms

Only those harms identified in the review protocol are reported here. See Figure 6 for detailed harms data.

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

Adverse Events

No information is available from the Weiss et al. (2013) study on the overall frequency of treatment-emergent AEs associated with trientine or DPA monotherapy.

Serious Adverse Events

No information is available from the Weiss et al. (2013) study on the overall frequency of treatment-emergent serious AEs associated with trientine or DPA monotherapy.

Withdrawals Due to Adverse Events

In the Weiss et al. (2013) study, treatment discontinuations due to AEs were more common with DPA (94 out of 326 treatments [28.8%]) compared with trientine (10 out of 141 treatments [7.1%]) (Figure 7). 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; the most common AEs (≥ 5% frequency in either group) that led to treatment discontinuation were arthralgia (29 out of 326 [8.9%] versus 4 out of 141 [2.8%]), increase in antinuclear antibodies (22 out of 326 [6.7%] versus 1 out of 141

Figure 6: Summary of Harms

	DPA (n = 326 analyzed)	Trientine (n = 141 analyzed)
Death related to adverse event	0	0
Number of treatments discontinued owing to adverse events	94 (28.8%)	10 (7.1%)
Adverse events leading to discontinuation		
Sicca symptoms	7 (2.1%)	
Fatigue	3 (0.9%)	
Pruritus	2 (0.6%)	1 (0.7%)
Gastric complaints (nausea, gastric pain)	8 (2.5%)	2 (1.4%)
Arthralgia	29 (8.9%)	4 (2.8%)
Myalgia	7 (2.1%)	1 (0.7%)
Cephalgia	4 (1.2%)	
Nephropathy	3 (0.9%)	1 (0.7%)
Albuminuria/proteinuria	20 (6.1%)	
Hematuria	2 (0.6%)	
Nephrotic syndrome	4 (1.2%)	
Elastosis cutis	9 (2.8%)	
Leukopenia	6 (1.8%)	1 (0.7%)
Increase of ANA antibodies	22 (6.7%)	1 (0.7%)
Erythema	11 (3.4%)	1 (0.7%)
Alopecia	1 (0.3%)	
Lupus erythematosus	3 (0.9%)	1 (0.7%)
Hirsutism	1 (0.3%)	1 (0.7%)
Development of psychiatric symptoms	5 (1.5%)	
Optic neuritis	1 (0.3%)	
Polyneuropathy	6 (1.8%)	
Other	16 (4.9%)	4 (2.8%)

ANA, antinuclear antibody.

DPA = d-penicillamine.

Source: Reprinted from Clinical Gastroenterology and Hepatology, Vol 11, Issue 8, Weiss KH, Thurik F, Gotthardt DN, et al., Efficacy and safety of oral chelators in treatment of patients with Wilson disease, pp1028 to 1035.E2, 2013 with permission from the American Gastroenterological Association.[13]

[0.7%]), and albuminuria or proteinuria (20 [6.1%] versus not reported) for DPA treatments versus trientine treatments, respectively. Rates of discontinuation for any reason were not statistically significantly different between the chelator treatments (P = 0.360), as reported in the publication.[13] The results of the Kaplan–Meier estimation for discontinuation of treatment due to any cause or due to AEs are illustrated in Figure 7.

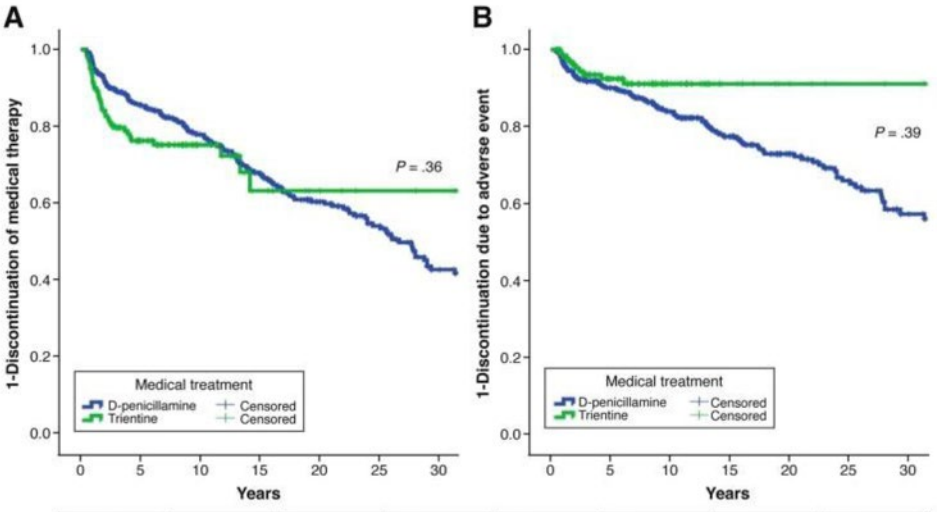
Mortality

No deaths were reported in the Weiss et al. (2013) study.

Notable Harms

The AEs of special interest identified in the protocol for the systematic review were rash, nephrotoxicity, polyneuropathy, pancytopenia, polymyositis, optic neuritis, and iron deficiency anemia. The only information available was from the Weiss et al. (2013) study, which reported the number of chelator monotherapy treatments discontinued due to AEs of special interest. There were 6 DPA treatments (1.8%) discontinued due to polyneuropathy compared to 0 reported for trientine. There were also more DPA treatments discontinued due to nephrotic syndrome (4 treatments [1.2%]) and albuminuria or proteinuria (20 treatments [6.1]) compared to 0 trientine treatments discontinued for these reasons. One trientine treatment (0.7%) and 6 DPA treatments (1.8%) were discontinued due to leukopenia.

Figure 7: Discontinuation of Treatment Due to Any Cause or Adverse Event (Weiss et al. [2013] Study)



At risk		5 years	10 years	15 years	20 years	25 years	30 years
DPA	326	254	202	150	110	79	47
Trientine	141	81	36	12	6	3	2

Note: There appears to be an error in the above published figure (B) as in the text and tabular data of the Weiss et al. (2013) publication the P value is reported as P = 0.039.

Source: Reprinted from Clinical Gastroenterology and Hepatology, Vol 11, Issue 8, Weiss KH, Thurik F, Gotthardt DN, et al., Efficacy and safety of oral chelators in treatment of patients with Wilson disease, pp1028 to 1035.E2, 2013 with permission from the American Gastroenterological Association.[13]

Critical Appraisal

Internal Validity

As a retrospective cohort analysis, the Weiss et al. (2013) study is limited by lack of randomization and the non-prospective collection of efficacy and harms outcomes. A major concern and source of bias with retrospective analyses is that patients were prescribed treatment based on their individual characteristics rather than being randomly allocated to treatment.[29] Another potential source of bias is that the researchers were reliant on past reporting of symptoms, clinical and laboratory parameters, and response to treatment by others who recorded information in patient records; thus, they were unable to prospectively identify specific efficacy outcomes or to control for confounders. A potential confounder could have been the availability of DPA or trientine, which would have influenced the choice and sequence of therapy. There was a more than 2-fold greater number of DPA treatments (N = 326) than trientine treatments (N = 141), with most DPA treatments (90.2%) used as first-line treatment compared to trientine (25.5%). This could have been due to a lack of access to trientine, and may have biased the harms results in favour of trientine. DPA is known to be poorly tolerated, and because most patients in the study received DPA, there was likely a higher probability that DPA treatment would result in more treatment discontinuations due to AEs.

This study was also not blinded. This may have introduced bias into the categorization of hepatic and neurologic outcomes, which were all subjectively assessed. The authors relied on the reporting of symptoms and hepatic and neurologic outcomes in patient records, which they later categorized subjectively as improved or worsened. The authors also identified patients subjectively as having hepatic, neurologic, or mixed presentation and hepatic patients as being symptomatic based on clinical or biochemical signs of liver disease. No criteria or rules regarding how decisions were made to categorize patients based on relative differences were stated. This could have introduced substantial reporting bias, although the direction of such bias is unknown. Improvement or worsening of neurologic disease was based on the physician's report in the patient record. As a result, the researchers were dependent on the treating physician's opinion of the outcome. The reporting of harms outcomes was also subject to reporting bias, given that the authors also categorized the reasons for treatment discontinuation subjectively, due to AEs.

The specific time frame of the study, or the calendar-year period over which the patients were treated, was not reported. If patients were treated during different chronologic time periods, it is possible that changes in clinical practice or the availability of treatment guidelines could have influenced choice of treatment. It was stated in the Weiss et al. (2013) publication that outcomes were based on the latest available follow-up evaluation within a 6-month to 48-month period. It follows, then, that the cumulative hepatic and neurologic outcomes reported in the study could comprise different treatment intervals ranging anywhere from 6 months to 48 months for different patients. It is not known how this may have affected the study outcomes or whether the cumulative treatment times were equal between trientine and DPA treatments. Further, it was reported that data on discontinuations and discontinuations due to AEs were collected over a median 13.3-year period to inform the Kaplan–Meier analysis, but no range of time over which these data were collected was reported. In addition, no further details were provided on the methodology of the Kaplan–Meier analysis, which makes these data difficult to interpret.

The reporting of results by number of chelator monotherapy treatments as opposed to the number of patients complicates the interpretation of the baseline patient characteristics and

of the efficacy and harms outcomes. It is difficult to ascertain if the baseline characteristics are balanced between the chelator treatments, or if differences in efficacy and harms outcomes are valid, because an individual patient could have been counted more than once in the results. Double data-counting compromises the validity of the dataset. For example, if an individual patient displays a specific characteristic — such as hepatic presentation of Wilson disease — and is double-counted, this may result in more treatments being associated with hepatic presentation than if patients were randomly selected and counted only once in the dataset. There were 405 patients included in the study, but results are reported for 467 chelator monotherapy treatments. The resulting inference is that up to 62 patients were counted more than once (e.g., as first- and second-line therapy).

There was no clear definition or validation of the efficacy outcomes in terms of reliability, validity, responsiveness, or MIDs, which makes interpretation of the efficacy results difficult. This is especially true regarding the relative differences between categories assigned by the authors (e.g., improved to normal versus improved but not normal).

The rate of treatment discontinuations was disproportionally higher with DPA treatment (43.6%) compared with trientine treatment (25.5%). No information was provided regarding patient follow-up after treatment discontinuation, and there was no imputation of missing data. Treatment discontinuations were analyzed using Kaplan–Meier estimation; however, over time, the number of treatments at risk in the trientine group are considerably smaller relative to the DPA group (e.g., 150 DPA treatments versus 12 trientine treatments at 15 years). This makes the interpretation of these data uncertain.

There were no pre-specified subgroups reported in the study methods; however, the authors categorized patients subjectively as symptomatic and according to first-line or second-line therapy, and subsequently reported hepatic and neurologic outcomes according to these subpopulations. No statistical adjustments to control for type I error were made for the multiple comparisons of hepatic and neurologic outcomes between the DPA and trientine treatment groups or among the apparent subgroups. Moreover, the sample sizes of certain subgroups were small (i.e., N = 13 or 20 treatments). This means caution is warranted in the interpretation of the results.

There were inconsistencies in the reporting of data in the study. For example, the abstract states that 471 chelator monotherapies were analyzed, but results are reported for 467 chelator treatments. In addition, the P value for the statistical assessment of the difference between trientine and DPA treatment for discontinuation due to AEs was reported to be P = 0.039 in a table and in the text of the publication; however, it was shown as P = 0.39 in the Kaplan–Meier curve depicting the same (Figure 7). Additionally, the time period for data on discontinuation and discontinuation due to AEs was stated to be a mean of 13.3 years and a median of 13.3 years in different sections of the publication, and no measure of variability (e.g., standard deviation) or range was reported with these data.

External Validity

There were no Canadian patients included in the Weiss et al. (2013) study. Patients were identified for inclusion from the patient records of tertiary hospitals in Germany and Austria as well as from the EUROWILSON patient registry. The clinical experts involved in the review advised that the baseline characteristics of the patients in the study were reasonably similar to the population of Canadian patients who would be candidates for trientine, with the possible exception of pediatric patients. The only age characteristic reported in the Weiss et al. (2013) study was the median age at diagnosis, which was 19.51 years (range = 1.23

years to 55.06 years) for trientine treatment and 17.51 years (range = 0.74 years to 60.05 years) for DPA treatment. As a result, it is not known how many pediatric patients less than 18 years of age were included in the study.

Although patients were identified as being asymptomatic or having hepatic, neurologic, or mixed presentation at initial diagnosis, the results were not reported according to these initial presentations. Most patients (51.1%) presented with hepatic symptoms, while another 22.7% presented with neurologic symptoms. This is similar to what would be expected in Canadian patients, according to the clinical experts on the review team. It was noted that some specialized clinics in Canada may predominantly treat patients with neurologic presentation because these clinics are considered to be centres of excellence for neurologic care.

Dosage and administration schedules for trientine and DPA were not reported in the study, so it is not known if the doses used were in alignment with Health Canada–approved doses of either drug. Additionally, it was not stated whether any patients who discontinued second-line therapy with DPA or trientine subsequently received a rechallenge with either of these, because only first- and second-line treatments were reported. The clinical experts consulted for this review indicated that it may be possible to rechallenge a patient on chelator therapy following prior discontinuation of chelator treatment, especially if the reason for discontinuation was not related to serious intolerance or toxicity. (For example, if a patient discontinued chelation therapy due to gastrointestinal upset, they could try it again using a different dosage.) The clinical experts cautioned that toxicity with DPA may be worse upon rechallenge.

Patients who received combination therapy with zinc (i.e., a chelator plus zinc therapy) were excluded from the study. According to the clinical experts consulted for this review, upon diagnosis of Wilson disease, patients are usually treated with chelators with or without zinc as first-line therapy. Moreover, zinc may be added to chelation therapy to address concerns about very excessive copper overload (to accelerate copper reductions) or to minimize the dose of a chelator (if intolerance or concern about worsening of neurologic symptoms is an issue). Patients receiving only zinc monotherapy over the treatment period were also excluded. According to the clinical experts, zinc is primarily used as a maintenance therapy after a period (usually 1 year) of chelation therapy. Zinc monotherapy may also be used as initial therapy for people diagnosed through sibling screening who have very limited copper overload or in patients with a primary neurologic presentation in whom chelators may worsen neurologic symptoms, sometimes irreversibly. Patients who received 6 months or less of chelator treatment were also excluded from the study. As a result, patients who underwent liver transplantation shortly after being diagnosed with Wilson disease were not included in the analyses. Therefore, the results of this study may not be generalizable to these patients.

No data were reported for key outcomes of clinical relevance to patients (based on the patient input received for this review), such as HRQoL and adherence. Additional outcomes included in the review protocol for which there also were no data included psychiatric manifestations, copper levels, and health care resource utilization. Thus, there is an evidence gap regarding many of the outcomes identified in the review protocol. It is not known whether the outcomes used in the study (i.e., hepatic and neurologic improvement and worsening) would be used by physicians in Canadian clinical practice (or whether the same interpretations would be made) because the authors of the study assessed these outcomes subjectively.

The duration of follow-up was 48 months, but Wilson disease requires continuous lifelong treatment. As a result, the length of follow-up may not have been adequate to capture the

long-term efficacy and harms outcomes of the treatments. A key outcome that was not reported — but could be addressed through longer follow-up — is patient adherence to treatment. Adherence to chelation therapy is vital to the effective treatment of Wilson disease. According to the clinical experts on the review team, poor adherence is the major reason for treatment failure in these patients.

Table 8 summarizes the generalizability of the evidence from the Weiss et al. (2013) study.

Discussion

Summary of Available Evidence

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 over a 48- month period. The second study (Study 17-VIN-0021) was an open-label, 2-period, 2-sequence, 2-treatment, crossover, single-dose, fasting bioequivalence study of trientine hydrochloride 250 mg capsules compared to Syprine (trientine hydrochloride) 250 mg capsules in 44 healthy adult male and female volunteers. The objective of this second study was to compare the rate and extent of absorption of trientine from the 2 formulations to determine if they were bioequivalent. Because the purpose of Study 17-VIN-0021 was to assess bioequivalence in healthy volunteers, not efficacy and safety in patients with Wilson disease, it was not reviewed in detail in this report.

According to the clinical expert on the review team, the baseline characteristics of the patients in the Weiss et al. (2013) study were reasonably similar to those of Canadian patients who would be candidates for trientine, with the possible exception of pediatric patients (< 18 years of age). The median age at diagnosis was 17.5 years for DPA treatment compared with 19.5 years for trientine treatment (the only age parameter reported in the study). Although patients less than 18 years of age were included, no details about the number or the ages of these patients were provided.

The Weiss et al. (2013) study reported baseline characteristics and efficacy and safety outcomes by number of chelator treatments (not by number of patients). At initial presentation, about half of the treatments (207 [51.1%]) were associated with hepatic symptoms only; 92 (22.7%) were associated with neurologic symptoms only; 52 (12.8%) were associated with mixed presentation (hepatic and neurologic symptoms); and 54 (13.3%) were asymptomatic. If these proportions broadly reflect patient presentations, the clinical experts advised that a similar distribution would be seen in Canadian clinical practice. The key limitations of the Weiss et al. (2013) study are its retrospective design, lack of randomization and blinding, absence of information about time frames, subjective assessment of outcomes, reporting of results by number of chelator treatments (rather than number of patients), and exclusion of patients who received zinc monotherapy or combination chelator therapy with zinc. There were no data available for most of the efficacy outcomes identified in the review protocol, including outcomes of interest to patients, such as HRQoL and adherence.

Table 8: Assessment of Generalizability of Evidence for Trientine

Domain	Factor	Evidence from the Weiss et al. (2013) study	CADTH's assessment of generalizability
Population	Age	The only age parameter reported was median age at diagnosis, which was 19.51 years (range = 1.23 years to 55.06 years) for trientine and 17.51 years (range = 0.74 years to 60.05 years) for DPA. It is not known how many pediatric patients (< 18 years) were included in the study.	Although it is not known how many pediatric patients were included, the study results are likely generalizable to pediatric patients (< 18 years), given that the age range of patients at diagnosis implies that pediatric patients were included. As further support, the clinical experts on the review team advised that there are no compelling reasons why trientine cannot be used in patients < 5 years of age.
	Disease status at presentation	Patients were categorized as asymptomatic (13.3%), hepatic (51.1%), neurologic (22.7%), or mixed hepatic and neurologic (12.8%) at initial presentation; however, the results were not reported by disease status.	According to the clinical experts, the study included all presentations of Wilson disease in proportions that would be expected among Canadian patients. In addition, other baseline patient characteristics were similar to those of Canadian patients. As a result, it is reasonable to assume that the results are generalizable to a wide range of patients with Wilson disease and to varying presentations.
Intervention	Trientine 500 mg/ day to a maximum of 2,000 mg/day orally on an empty stomach in divided doses 2 to 4 times a day	No information on the dose of trientine or the administration schedules was provided in the study.	In the absence of this information, it is not possible to determine if the dose and administration schedule of trientine was aligned with the Health Canada–approved dosage for trientine.
	First-line or second- line use	Treatments were categorized as first- or second-line. However, no systematic criteria for doing so were reported in the study.	Hepatic and neurologic outcomes were reported for trientine by first- and second-line. As a result, the results are generalizable to these lines of treatment. No information was provided on third- line treatment or beyond, or on rechallenge with chelator therapy.
Comparator	DPA 750 mg/day to 1,500 mg/day on an empty stomach at least 1 hour before meals or 2 hours after meals and at least 1 hour apart from any other drug, food, or milk	No details about the dose of DPA or the administration schedule were provided in the study.	In the absence of this information, it is not possible to determine if the dose and administration schedule of DPA was aligned with the Health Canada–approved dosage for DPA.

Domain	Factor	Evidence from the Weiss et al. (2013) study	CADTH's assessment of generalizability
(continued)	First- or second- line use	Treatments were categorized as first- or second-line, but no systematic criteria for doing so were reported in the study.	Hepatic and neurologic outcomes were reported for DPA by first- and second-line use; therefore, the results are generalizable to these lines of treatment. No information was provided on third- line treatment or beyond, or on rechallenge with chelator therapy.
Outcomes	Appropriateness of outcomes	Outcomes included hepatic and neurologic worsening or improvement; however, no details were provided regarding what comprised a hepatic or neurologic outcome.	The clinical experts advised that the outcomes were appropriate, but little detail was provided as to what comprised the hepatic and neurologic outcomes or what criteria or rules were considered in the assessment of improvement or worsening.
	Criteria used to define response	No criteria or rules to define response or relative differences in response were provided.	It is not possible to comment on the generalizability of the definition of response criteria because this information was not provided in the study.
Settings	Trial sites	The study included patients identified from tertiary care centres in Germany and Austria, and from the EUROWILSON patient registry. No Canadian patients were included.	Although no Canadian patients were included, the clinical experts consulted on the review agreed that the baseline patient characteristics of the patients enrolled in the study were reasonably similar to those of the population of Canadian patients who would be candidates for trientine, with the possible exception of pediatric patients.
	Supportive medication	Patients who were on combination zinc + chelator therapy were excluded from the study, as were patients who were on zinc monotherapy.	Canadian patients are usually treated with chelators, with or without zinc as first-line therapy. Moreover, zinc may be added to chelation therapy to address concerns about very excessive copper overload (to accelerate copper reductions) or to minimize the dose of a chelator (if there is intolerance or concern about worsening of neurologic symptoms). Because patients on combination chelator plus zinc or zinc monotherapy were excluded from the study, the results are not generalizable to these patients.

Interpretation of Results

Efficacy

The Weiss et al. (2013) study evaluated 467 chelator-based treatment regimens with durations of 6 months to 48-months. Of these regimens, 141 (30.2%) were trientine treatments and 326 (69.8%) were DPA treatments. Of the trientine treatments, 36 (25.5%) were used as first-line treatments and 105 (74.5%) were used as second-line treatments, compared to 294 (90.2%) and 32 (9.8%) first- and second-line DPA treatments, respectively. The disproportionate use of DPA as a first-line treatment may be due to lack of access to trientine, rather than to trientine being reserved for use as a second-line option for patients

intolerant to DPA. The clinical experts consulted for this review advised that there is no compelling reason that trientine cannot be used as a first-line therapy in patients with Wilson disease. It may, in fact, be the preferred choice due to its better tolerability profile. The lack of randomization and stratification of patients according to first- and second-line use of trientine or DPA at study entry resulted in a substantial baseline imbalance for the proportion of treatments used as first-line, which was statistically significant ($P < 0.001$), as reported in the publication.[13] The reporting of baseline patient characteristics and efficacy and harms outcomes by number of chelator monotherapy treatments, as opposed to by number of patients, also complicates the interpretation of baseline imbalances and relative treatment effects because individual patients may have been double-counted in the results (i.e., for first- and second-line treatment); however, the direction of bias is difficult to ascertain.

This study was also not blinded. This fact may have introduced bias into the assessment and categorization of the hepatic and neurologic outcomes and reasons for treatment discontinuation. Because the data were not collected prospectively, the researchers relied on non-standardized reporting by others in patient records, from which they derived clinical and laboratory information. Using this information, they assessed and categorized patients subjectively as being symptomatic or having improved or worsening hepatic and neurologic outcomes. Hepatic outcomes were based on clinical symptoms, liver enzymes, and liver function tests. Patients with clinical or biochemical evidence of liver disease were considered symptomatic. No details were provided as to what criteria or rules were followed to categorize patients as improved or worsened. This absence of detail, coupled with the lack of validation of these outcomes or the identification of MIDs, makes it challenging to interpret the results. Hepatic improvement scores following either first-line or second-line treatment were similar between trientine and DPA and no statistically significant differences were identified between the treatments either in all patients or in only symptomatic patients. Hepatic improvement scores were lower during second-line treatment with both drugs; the scores were not statistically significantly different between the 2. Similar proportions of trientine and DPA treatments (first- or second-line) were categorized as stable disease (defined as unchanged hepatic symptoms); these proportions were reported for symptomatic patients only. Hepatic deterioration or worsening was reported for 4 DPA first-line treatments and 4 trientine second-line treatments in all patients and in symptomatic patients, which suggests the 4 treatments may represent the same patients. There was no hepatic worsening in any patients (all or symptomatic) who received trientine as first-line therapy or DPA as second-line therapy. Improvement in hepatic symptoms with either trientine or DPA treatment is in line with the observations of the clinical experts involved in this review, given that most patients with Wilson disease who present with hepatic symptoms are expected to have their hepatic symptoms respond well to chelation therapy.

The course of neurologic disease was based on physician evaluations of neurologic symptoms as reported in the patient records. The researchers also categorized neurologic outcomes in a similar manner as hepatic outcomes, although no additional details were provided. Neurologic improvement scores were similar between trientine and DPA following first-line treatment in both the all-patient and symptomatic-patient groups, and the differences between treatments were not statistically significantly different. For second-line treatment, numerically fewer DPA treatments (3 out of 31 [9.7%] and 3 out of 13 [23.1%]) were associated with neurologic improvement compared with trientine treatments (26 out of 103 [25.2%] and 26 out of 51 [51.0%]) for all and symptomatic patients, respectively; however, the differences were not statistically significantly different. It must be noted that only 3 second-line DPA treatments contributed to these analyses; therefore, these results warrant

cautious interpretation. Rates of neurologic worsening were low and comparable between trientine and DPA when used as second-line treatments, with no statistically significant differences identified between the treatments; however, the numbers of patients included in these analyses were small. Importantly, the proportion of first-line treatments that resulted in neurologic worsening was statistically significantly higher with trientine than with DPA for all patients (4 out of 38 treatments [10.5%] versus 6 out of 295 treatments [2.0%], respectively; P = 0.018) and for symptomatic patients (4 out of 20 treatments [20.0%] versus 6 out of 114 treatments [5.3%], respectively; P = 0.042). It is unclear why a higher proportion of trientine first-line treatments would have led to worsening of neurologic symptoms compared to DPA. However, the clinical experts on the review team advised that a transient elevation of serum copper following the initiation of any chelator treatment can potentiate irreversible neurologic symptoms in patients with Wilson disease who have neurologic presentation. Stable neurologic disease was observed in similar proportions of trientine and DPA treatments after first-line treatment; however, following second-line treatment, a larger proportion of DPA treatments (9 out of 13 [69.2%]) than trientine treatments (17 out of 51 [33.3%]) were categorized as stable. No statistical comparison was reported.

The results of Study 17-VIN-0021 demonstrated that Waymade-Trientine (test) is bioequivalent to Syprine (reference) in accordance with Health Canada bioequivalence standards.[30] Bioequivalence implies that the test product can be expected to have the same therapeutic effects and safety profile as the reference product when administered to patients under the conditions specified in the labelling.[30] In its decision to approve Waymade-Trientine, Health Canada considered that the results of Study 17- VIN-0021 supported the assertion that Waymade-Trientine is representative of Syprine, which is authorized for use in the US and has been used in studies reported in the literature.[31] Moreover, the clinical expert consulted by CADTH confirmed that Syprine (obtained through the Health Canada SAP) was used in Canada before the termination of the SAP. Thus, Study 17-VIN-0021 provides evidence that Waymade-Trientine is bioequivalent with a reference product that has been used in clinical practice in Canada for the treatment of Wilson disease.

It is evident that there is very low-quality evidence to support the efficacy of trientine for the treatment of Wilson disease. Although the literature search failed to identify any relevant studies for inclusion in this review, it did identify 2 systematic reviews of common therapies for Wilson disease.[32,33] The first was a systematic review and meta-analysis that included 2 studies of trientine (i.e., the Weiss et al. [2013] study and a study by Czlonkowska et al. [2005] that compared trientine and tetrathiomolybdate, which is not approved in Canada).[13,34] The studies were deemed to be of low quality and to have insufficient evidence to perform a meta-analysis; however, it was noted that the studies reported no difference in effectiveness of primary outcomes. Neurologic deterioration occurred more frequently with trientine versus DPA or tetrathiomolybdate, and the relative risk for AEs was lower in trientine therapy.[32] The second systematic review sought to evaluate the clinical efficacy of chelator drugs and zinc in the initial treatment of Wilson disease; however, no relevant studies of trientine were identified for inclusion.[33] Despite the limited evidence, the use of trientine in Wilson disease must be considered in the context of the long market availability of trientine worldwide, (i.e., since the 1960s) and the history of trientine use in Canada through the Health Canada SAP. For evidence of the clinical efficacy of trientine, the Health Canada approval of Waymade-Trientine relied on the published literature (most notably the Weiss et al. [2013] study) and market experience.[31] An additional consideration is that the clinical pharmacology of trientine is relatively simple: its mechanism of action represents a rational approach for the treatment of a disease caused by excess copper accumulation because it is a copper-chelating drug that

forms a stable copper complex that is readily eliminated by the kidneys. Moreover, evidence of its pharmacologic effect is directly measurable by urinary copper excretion.

There are numerous evidence gaps pertaining to the use of trientine for Wilson disease. No Canadian patients were included in the identified studies; there were no data available for most of the efficacy outcomes identified in the review protocol (including those of interest to patients); and there were no studies identified in pediatric patients, despite the Health Canada approval of trientine for patients 5 years of age and older. A recent retrospective cohort analysis of 182 children (mean age = 10.7 ± 4.2 years) with Wilson disease included in a national Wilson disease registry in France from 1995 to 2019 reported that most children (84.6%) had hepatic presentation at diagnosis, while 10.4% had neurologic manifestations and 4.9% were asymptomatic.[14] The diagnosis and treatment of Wilson disease in children can be challenging because children often do not display the same clinical and laboratory hallmarks as adults, especially when it comes to neurologic manifestations. Most children (72%) in the registry received DPA as first-line therapy, followed by zinc (13%) and trientine (9%). Overall survival after 20 years of follow-up was 98%, supporting the notion that diagnosis at early stages of liver disease and proper treatment of Wilson disease result in excellent outcomes. There were also no data available for the use of trientine plus zinc, which is a frequently used combination in specific clinical conditions, as described in the Clinical Input section of this report. These and other factors may affect the generalizability of the results of the Weiss et al. (2013) study to Canadian patients with Wilson disease, as detailed in Table 8. Despite these limitations, these evidence gaps must be weighed against the fact (as reiterated by the clinical experts) that currently, Canadian patients with Wilson disease who fail on or cannot tolerate DPA have no alternative chelator option. If these patients do not receive de-coppering treatment, their disease is ultimately fatal.

Harms

There are limited harms data available for trientine in patients with Wilson disease; the only source of harms data identified in patients was the Weiss et al. (2013) study. In this study, the only harms outcome reported was the proportion of trientine or DPA treatments discontinued due to AEs. Treatment discontinuation due to AEs was more common with DPA (94 out of 326 treatments [28.8%]) than with trientine (36 out of 141 treatments [7.1%]); the difference was statistically significant (P = 0.039), as reported in the publication.[13] Although treatment discontinuations due to any cause were also higher with DPA (142 out of 326 treatments [43.6%]) than with trientine (36 out of 141 treatments [25.5%]), the difference was not statistically significantly different (P = 0.36).[13] The main reasons for discontinuation due to AEs were arthralgia, increase in antinuclear antibodies, and albuminuria or proteinuria, all of which were numerically higher with DPA versus trientine treatments. The harms results may have been biased due to the disproportionate number of DPA treatments (N = 326) compared to trientine treatments (N = 141) and because most DPA treatments (294 out of 326 [90.2%]) were first-line. DPA is known to be poorly tolerated; given that most patients in the study received it, there was likely a higher probability that DPA treatment would result in more treatment discontinuations due to AEs than trientine. Nonetheless, the clinical experts on the review team advised that the poor tolerability of DPA is well known and that 20% to 40% of patients cannot take it due to toxicity or intolerance.

Trientine is considered to be generally well tolerated, with the most common initial AEs being self-limiting nausea and occasional occurrences of skin rash and anemia. The Canadian product monographs for Waymade-Trientine and MAR-Trientine both contain serious warnings and precautions (i.e., black box warnings) stating that trientine should only be

initiated by physicians experienced in the management of Wilson disease and that worsening of neurologic or neurocognitive functioning, which can be irreversible, may occur in patients with pre-existing neurologic and/or neuropsychiatric impairment due to Wilson disease who are treated with trientine.[11,35] The product monographs recommend that the initiation of trientine should be carried out with caution in patients with pre-existing neurologic and/or neuropsychiatric impairment, and only after careful consideration of all available treatment options and an acceptable benefit-risk analysis. Close monitoring of clinical response in these patients is required in the first few months following the initiation of trientine.[11,35] Health Canada has noted that patients with pre-existing neurologic and/or neuropsychiatric impairment may respond adversely to the early increases in serum copper concentrations that are often observed after trientine initiation due to its action on the mobilization of copper from central stores. Because these patients have sustained damage to the blood-brain barrier from past exposure to excessive serum copper levels, they are vulnerable to adverse neurologic effects from temporarily elevated serum copper levels.[31]

Conclusions

A retrospective cohort analysis of mainly adult patients with Wilson disease demonstrated that the efficacy of trientine is comparable to that of DPA for improving hepatic and neurologic outcomes when used as first-line therapy, and when used as second-line therapy in patients who have failed or were intolerant to DPA. First-line treatment with trientine was associated with statistically significantly higher rates of neurologic worsening than DPA, but not when used as second-line treatment. More DPA treatments than trientine treatments were discontinued due to AEs, which was statistically significant. Due to the low quality of this study, there is considerable uncertainty in the relative estimates of efficacy and harms between trientine and DPA. Despite the limitations, this study comprises the largest body of evidence to date for the use of trientine in Wilson disease. Although the evidence is very limited, this must be placed in the context of the long market history of trientine worldwide and the experience gained in Canadian patients who received trientine through the Health Canada SAP. The mechanism of action of trientine also represents a rational approach for the treatment of a disease caused by excess copper accumulation. Despite the many limitations associated with the evidence, Canadian patients with Wilson disease who fail on or cannot tolerate DPA currently have no alternative chelator option other than trientine. Untreated Wilson disease is associated with high morbidity and mortality.

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Appendix 1: Patient Group Input

Note that this appendix has not been copy-edited.

CLF – Trientine Hydrochloride (Waymade-Trientine)

About Your Patient Group

Founded in 1969, the 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, preventive 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.

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 through CLF communication channels. A total of 8 respondents provided input for this submission: 5 patients and 3 caregivers. A total of 3 patients were from Ontario and 2 from Manitoba. Two caregivers were from Nova Scotia and 1 was 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 includes in this submission is input from 2 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.

Disease Experience

Wilson disease is a hereditary disease in which excessive amounts of copper accumulates 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 1950s and 1960s, 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 affected day-to-day activities. Caregivers have indicated that their ability to work and travel has been affected:

"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

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 drug. 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 drug 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 drug 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 2, 3, or 4 times daily. This may be increased to a maximum of 2000 mg/day for adults or 1,500 mg/day for pediatric patients aged 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 comorbidity 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 behavioural control can further affect patients' social lives, 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 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

Improved Outcomes

Trientine is a chelating drug 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 HCPs.

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 HCPs have highlighted barriers and limitations in accessing treatments for their Wilson disease. This included various financial challenges, issues with the SAP 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, and HCPs have highlighted barriers and limitations in accessing treatments for their Wilson disease. This included various financial challenges, issues with the SAP 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 lifesaving 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

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.

Dosage evaluations and/or intervals between dose have 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 2, 3, or 4 times daily. This may be increased to a maximum of 2,000 mg/day for adults or 1,500 mg/day for pediatric patients aged 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

Companion Diagnostic Test

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

Anything Else?

The CLF 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 HCPs. 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 lifesaving 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

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.

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 HCPs who responded to the CLF's online survey.

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 HCPs who responded to the CLF's online survey.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

The 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.

Table 9: Conflict of Interest Declaration for Patient 1

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In excess of $50,000
NA	–	–	–	–

Name: Nem Maksimovic

Position: Manager, National Health Promotion and Education Patient Group: CLF

Date: July 23, 2021

Appendix 2: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search update: September 13, 2021

Alerts: Weekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- Publication date limit: None
- Humans
- Language limit: None
- Conference abstracts: excluded

Table 10: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number

Syntax	Description
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

Searches:

1. trientine/
2. (trientine* or Cuprior* or Cufence* or Clovique* or Syprine* or SJ76Y07H5F or 7360ure56Q or hc3nx54582).ti,ab,rn,ot,nm,kf.
3. (AI3-24384 or Araldite* or "BRN 0605448" or BRN0605448 or CCRIS 6279 or CCRIS6279 or DEH 24 or DEH24 or EINECS 203-950-6 or EC 203-950-6 or HSDB 1002 or HSDB1002 or HY 951 or HY951 or NSC 443 or NSC443 or Tecza* or Trientina* or Trientinum* or Triethylene or cuprid or laszarin* or mk681 or mk 681 or mk0681 or "mk 0681").ti,ab,rn,ot,nm,kf.
4. 1 or 2 or 3
5. 4 use medall
6. Hepatolenticular Degeneration/
7. (hepatolenticular* or hepatocerebral* or neurohepat* or (wilson* adj3 (disease* or syndrome* or degenerat* or morbus)) or (westphall adj2 strumpell) or pseudoscleros* or pseudo-scleros* or (copper adj3 (storage or remov* or deplet* or chelat*)) or progressive lenticul*).ti,ab,kf.
8. 6 or 7
9. 8 use medall
10. 5 and 9
11. *trientine/
12. (trientine* or Cuprior* or Cufence* or Clovique* or Syprine*).ti,ab,dq,kw.
13. (AI3-24384 or Araldite* or "BRN 0605448" or BRN0605448 or CCRIS 6279 or CCRIS6279 or DEH 24 or DEH24 or EINECS 203-950-6 or EC 203-950-6 or HSDB 1002 or HSDB1002 or HY 951 or HY951 or NSC 443 or NSC443 or Tecza* or Trien or Trientina* or Trientinum* or Triethylene* or cuprid or laszarin* or mk681 or mk 681 or mk0681 or "mk 0681").ti,ab,dq,kw.
14. 11 or 12 or 13
15. 14 use oemezd
16. Wilson disease/
17. (hepatolenticular* or hepatocerebral* or neurohepat* or (wilson* adj3 (disease* or syndrome* or degenerat* or morbus)) or (westphall adj2 strumpell) or pseudoscleros* or pseudo-scleros* or (copper adj3 (storage or remov* or deplet* or chelat*)) or progressive lenticul*).ti,ab,kw.
18. 16 or 17
19. 18 use oemezd
20. 15 and 19
21. conference abstract.pt.
22. conference review.pt.

23. 21 or 22

24. 20 not 23 25. 10 or 24

25. remove duplicates from 25

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

Search -- Studies with results | [trientine AND Wilson's Disease]

WHO International Clinical Trials Registry Platform

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

Search terms -- | [trientine AND Wilson's Disease]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

Search terms -- sleep apnea*, | [trientine AND Wilson's Disease]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms -- sleep apnea*, | [trientine AND Wilson's Disease]

Grey Literature

Search dates: August 09 – August 13, 2021

Keywords: trientine, Wilson's Disease

Limits: No limits used.

Updated: Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching *Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics

- Internet Search
- Open Access Journals

CADTH

Pharmacoeconomic Review

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Abbreviations

AE	adverse event
ALD	advanced liver disease
BIA	budget impact analysis
CHB	chronic hepatitis B
CHC	chronic hepatitis C
DPA	d-penicillamine
ICER	incremental cost-effectiveness ratio
QALY	quality-adjusted life-year
SAP	Special Access Program
SWD	stable Wilson disease
WWD	worsening Wilson disease

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Trientine hydrochloride (Waymade-Trientine), oral capsules
Submitted price	Trientine hydrochloride 250 mg: $20.00 per capsule
Indication	For the treatment of patients with Wilson disease who are intolerant to penicillamine
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	April 20, 2021
Reimbursement request	As per indication
Sponsor	Waymade PLC
Submission history	Previously reviewed: No

NOC = Notice of Compliance; PLC = public limited company.

Table 2: 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
Comparator	75 mg daily oral zinc, followed by no treatment for patients 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)

Component	Description
Key limitations	No treatment is unlikely to represent the current standard of care. The clinical evidence regarding the efficacy and tolerability of trientine is limited due to the lack of randomized trials. The proportions of patients who will progress to ALD, liver transplantation, or death are uncertain. The modelled population is not consistent with that of the Health Canada indication or the 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. The modelled costs and utilities did not change over time, but utilities tend to decrease because people age; in addition, post-liver transplantation 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 typically diagnosed and begin treatment. The mean dose of trientine that will be used in clinical practice is uncertain.
CADTH reanalysis results	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 with ALD die, and increased the proportion of patients with 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 ALD. 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 of less than $50,000 per QALY. CADTH was unable to address the absence of neurologic symptoms in the model, the lack of an active comparator, or the increased risks associated with nonadherence.

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

Conclusions

The clinical evidence regarding the use of trientine for the treatment of Wilson disease is associated with limitations due to the lack of randomized controlled trials or large observational studies. Despite this, trientine has been used for decades internationally and in Canadian patients who have received it through the Health Canada Special Access Program (SAP). Currently, for patients who fail on d-penicillamine (DPA) or cannot tolerate DPA, there are no alternative chelation treatments other than trientine. According to experts consulted for this review, untreated Wilson disease will generally progress to irreversible and likely fatal hepatic and/or neurologic harm.

Due to the absence of evidence, CADTH was unable to produce a reliable base-case analysis. As an exploratory analysis, CADTH removed zinc from the treatment paradigm to align with the indicated Health Canada population, 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 with ALD die, and increased the proportion of patients with ALD who receive a liver transplant. In this exploratory analysis, the incremental cost-effectiveness ratio (ICER) associated with the use of trientine in patients with Wilson disease who do not respond to or cannot tolerate DPA was $146,927 per quality-adjusted life-year (QALY) at the submitted price of $20 per 250 mg capsule. At this ICER, a 46.5% price reduction would be required to achieve an ICER of less than $50,000 per QALY. Crucially, this analysis assumes that in the absence of trientine, there are no viable treatment alternatives available to patients who fail on DPA, and that patients experience worsening symptoms immediately upon discontinuing DPA. Because patients are left untreated, the majority will experience acute liver failure, resulting in significant QALY losses under even the most conservative scenarios explored by CADTH. Annual treatment costs with trientine are high — up to $58,400 per patient — and are lifelong due to the chronic nature of the condition. Coupled with the absence of reliable clinical evidence, this makes the assessment of cost-effectiveness uncertain and heavily reliant on expert opinion.

CADTH was unable to adjust for other limitations, including the paucity of clinical and economic evidence, the exclusion of neurologic symptoms in the model, and the assumption of 100% adherence in a young population on a treatment regimen that is difficult to tolerate.

CADTH has previously reviewed another generic trientine product at the same submitted price. It is difficult to directly compare the results of the current model with those of the model from the previous submission because of differences in the structure and inputs of the models. Given that the clinical safety and effectiveness of the 2 brands are presumably the same — and the submitted prices were the same — any conclusion regarding the cost-effectiveness of 1 product would be expected to hold for the other.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinician groups, and drug plans that participated in the CADTH review process. Feedback from clinician groups was not received for this submission.

Feedback was received from the Canadian Liver Foundation. It was collected through an online questionnaire to which 8 patients and 5 caregivers responded. Additional information was received from 2 health care providers. Wilson disease was associated with emotional and psychological effects that affected the ability to exercise, work, travel, complete household activities, socialize, and fulfill family obligations. Additionally, feelings of constant stress and fear — and psychiatric symptoms, such as bipolar disorder, anxiety, and depression — were described.

Patients reported experience with zinc, DPA, and trientine. Respondents reported fatigue, appetite loss, nausea, and pain as side effects that were completely to somewhat intolerable, and fever, dizziness, forgetfulness, and stomach irritation as side effects that were somewhat to very tolerable. Respondents noted these side effects were significant enough to affect their quality of life. They reported additional stress associated with accessing medication, which reportedly could take months; denial of coverage could cause financial hardship. Two

patients and 2 caregivers reported having experience with trientine, accessed through private insurance after a challenging process.

All respondents reported that trientine was either effective or very effective at managing Wilson disease, and that the side effects they experienced were mainly stomach irritation, fatigue, and minor pain. One of the health care professionals emphasized the need for quick and affordable access to treatment for Wilson disease, reporting that 1 of their patients had been denied access to trientine, developed cirrhosis, and was awaiting a liver transplantation. The other indicated that without reimbursement, trientine remains out of reach for patients with Wilson disease.

Drug plans identified the following concerns related to the implementation of trientine: the inclusion of zinc as second-line therapy; the potential for physicians to want to access trientine as first-line therapy without a trial of DPA; and the lack of evidence in patients under 5 years of age. The plans expressed a desire to see the price of Waymade-Trientine compared to the price of trientine previously accessed through the Health Canada SAP. They were also concerned that the budget impact likely underestimates the number of eligible patients in Canada.

Several of these concerns were addressed in the sponsor's model:

- The effect of treatment on hepatic outcomes and quality of life.
- The relative tolerability of trientine.

In addition, CADTH addressed some of these concerns as follows:

- The removal of zinc from the modelled treatment pathway.
- Increasing the number of patients eligible for trientine therapy in the BIA.

CADTH was unable to address the following concerns raised from stakeholder input:

- The effect of trientine on psychological or neurologic outcomes in the assessment of cost-effectiveness.
- Comparing the cost of trientine at the currently submitted price to that previously paid through the SAP.

Economic Review

The current review is for trientine (Waymade-Trientine) for the treatment of patients with Wilson disease who are intolerant to penicillamine.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis in which zinc therapy followed by trientine 250 mg capsules for non-responding patients was compared to zinc therapy followed by no treatment in patients (aged 42 years) with Wilson disease who are intolerant to DPA. This treatment sequence differs from the Health Canada indication, which specifies that trientine

is indicated for the treatment of patients who are intolerant to DPA, but does not suggest that zinc be used between DPA and trientine.

The recommended starting dose of trientine for adult patients is 750 mg given in divided doses 2 to 4 times daily. The daily dose may be increased gradually to a maximum of 2,000 mg daily, if required. The starting dose for patients aged 5 years to 17 years is 500 mg per day in 2 to 4 daily doses, with a maximum recommended dose of 1,500 mg per day for patients aged 12 or under.[1] At the submitted price of $20.00 per 250 mg capsule, the annual cost of therapy with trientine ranges from $21,900 to $58,400 for adult patients, $14,600 to $58,400 for adolescents aged 13 years to 17 years, and $14,600 to $43,800 for children aged 5 years to 12 years.

For the base case, the sponsor estimated costs and QALYs for each treatment regimen from the perspective of a Canadian health care payer, over a lifetime time horizon, using a 1.5% annual discount rate for both costs and QALYs.

Model Structure

The sponsor submitted a Markov model with 6-month cycles in which all patients enter the model with stable Wilson disease (SWD) symptoms, having become intolerant to DPA and begun zinc therapy (Figure 1).[2] Patients could then transition to worsening Wilson disease (WWD) symptoms, at which point they discontinued zinc therapy and either continued in the WWD health state without further treatment or began trientine therapy and returned to the SWD health state. Patients on trientine could either continue in the SWD health state or transition once again to the WWD health state, discontinuing trientine and receiving no further treatment. All patients before this point had a risk of death per cycle consistent with age- and gender-matched Canadian mortality rates.[3] Once patients in either treatment group were in the WWD health state, they could transition to the advanced liver disease (ALD) health state, from which they could transition either to liver transplantation or death. Patients receiving a liver transplant could either die within 6 months or live out the remainder of their lives without further worsening of their Wilson disease symptoms.

Model Inputs

Patients entered the model at 42 years of age, as reported in the Weiss et al. (2019) study, with 32.7% being male.[4] Patients then transitioned to the WWD health state based on all-cause zinc discontinuation data from Weiss et al. (2013)[5] using a generalized gamma distribution to extrapolate discontinuation rates over a lifetime (Figure 2). Patients with WWD were assumed to discontinue zinc therapy. They could either remain on no therapy or begin treatment with a mean of 1,000 mg of trientine daily in the following cycle, returning to the SWD health state; those on no therapy remained in the WWD health state. Patients receiving trientine could then transition back to the WWD health state based on all-cause trientine discontinuation data from Weiss et al. (2011). A generalized gamma distribution was used to extrapolate discontinuation rates over a lifetime (Figure 3).

In each 6-month cycle, patients with WWD had a 5.73% chance of progression to ALD. This figure was derived from a 2010 UK study of patients with compensated cirrhosis between 1987 and 2002.[6] Once in the ALD health state, patients had a 10.34% risk of death per 6-month cycle (based on the annual rate observed in patients with decompensated cirrhosis in the same UK study[6]) and a 3.97% probability of undergoing a liver transplantation (based on a US study of patients with alcohol-associated liver disease in 2002 to 2010[7,8]). Among patients who received a liver transplant, 7.06% were assumed to die within 6 months, based

on a 2018 US study of first-time liver transplant recipients from 2002 to 2016.[9] Thereafter, patients who had received a liver transplant lived out the remainder of their lives without further worsening of Wilson disease symptoms, but with a mortality ratio 5.8 times higher than age- and gender-comparable Canadian averages, based on a 2015 study of Nordic patients who received liver transplant from 1985 to 2009 and survived 1 year afterward.[10]

A health-related utility of 0.838 was assigned to patients in the SWD state, based on Visual Analogue Scale scores from Weiss et al. (2019).[4] Patients in the WWD health state were assigned a utility of 0.751; those in the ALD state were assigned a utility of 0.602; and those who were post-liver transplantation were assigned a utility of 0.657, based on a recent Canadian meta-analysis of patients with chronic hepatitis C (CHC) who had mild or moderate CHC, decompensated cirrhosis, or were post-liver transplantation, respectively, standardized to the EuroQol 5-Dimensions 3-Levels questionnaire.[11] Patients could experience adverse events (AEs) associated with treatment: there was a 4.8% chance for zinc patients to experience arthralgia and skin rash, and a 16.3% or 2.3% chance for trientine patients to experience nausea and abdominal discomfort or fatigue, respectively. These AEs were associated with disutilities of 0.0270 for arthralgia, 0.0565 for nausea, 0.032 for skin rash, and 0.036 for fatigue. No disutility was associated with the act of undergoing liver transplantation.

Costs included the drug acquisition costs of trientine; zinc, as an over-the-counter supplement, was assumed not to have a cost paid by publicly funded drug plans. Monitoring of SWD was assigned $416 in costs per cycle and included 2 gastroenterology visits per year; urine and serum copper tests yearly; urinalysis, a liver panel, a complete blood count, a liver ultrasound, and an endoscopy twice per year; and a neurologic MRI every 2 years, based on expert consultation elicited by the sponsor and Schilsky 2017.[2,12] Patients experiencing hepatic worsening had $1,564 in monitoring costs per cycle; patients in the ALD state had $8,013 in monitoring costs per cycle; and post-transplantation patients accrued $27,293 in costs per cycle, all inflated from a 2004 Canadian costing study by Gagnon et al. of chronic hepatitis B (CHB) patients, CHB patients with decompensated cirrhosis, and CHB patients post-transplantation, respectively.[13] A 1-time cost of $106,331 was also applied at the time of transplantation, based on data from the Ontario Case Costing Initiative.[14]

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted a probabilistic analysis of 1,000 iterations. The results of the deterministic analysis were very similar to the probabilistic analysis. The probabilistic findings are reported in this section.

Base-Case Results

The sponsor concluded that, when used after a trial of oral zinc therapy in patients with Wilson disease who are intolerant to DPA, compared to a trial of zinc therapy followed by no treatment, trientine was associated with $322,049 in increased costs, yielding an additional 5.86 QALYs, for an ICER of $54,967 per QALY (Table 3). More details can be found in Table 10.

Sensitivity and Scenario Analysis Results

The sponsor conducted a series of scenario analyses, including lowering the age at model entry to 20 years; varying the probabilities of progressing to ALD, undergoing liver transplantation with ALD, and dying with ALD; and varying the acute mortality rate after liver transplantation and the mortality ratio relative to the general population after liver transplantation. The sponsor also used alternate utilities associated with hepatic worsening, varied the discount rate and the mean daily dose of trientine, and considered a societal

perspective. The ICERs associated with these scenario analyses all ranged from $36,546 to $72,787 per QALY gained, with both extremes of the range being associated with differing doses of trientine.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis.

- **No treatment is likely not the current standard of care:** The sponsor modelled the cost-effectiveness of trientine therapy compared to no treatment. However, the clinical experts consulted by CADTH indicated that patients with Wilson disease would never be left untreated. Patients who were intolerant to DPA or trientine would at least receive zinc; both DPA and trientine may also be reattempted at lower doses and with more adherence support. Compassionate access to tetrathiomolybdate,[15] which is still considered experimental and not marketed in Canada, might also be sought. Ideally, the cost-effectiveness of trientine compared to zinc therapy would be modelled. Given that zinc can be effective for some patients and would not incur drug plan costs (because it is an over-the-counter product), the ICER for trientine when compared to zinc would be higher than that reported when compared to no treatment. However, only non-randomized data exist regarding the efficacy and tolerability of zinc therapy for Wilson disease. In its submission, the sponsor assumed that patients continue to respond to zinc at a rate extrapolated from the continuation rates seen in Weiss et al. (2011).[16] However, this study is a retrospective analysis of patients who were deemed appropriate to receive zinc therapy. This includes patients who were asymptomatic or had a neurologic presentation only. Therefore, this population is not reflective of all patients with Wilson disease who are intolerant to DPA, and the estimate of efficacy is not useful to the decision problem analyzed in this submission.
    - CADTH was unable to adjust for this limitation in its reanalysis. The ICER associated with the comparison of trientine to zinc therapy would be higher than that reported when trientine is compared to no treatment, but the magnitude of this difference is unknown. If a subset of patients who respond to zinc could be reliably identified, then it would not be cost-effective to use trientine on these patients.
- **Clinical evidence is limited:** The efficacy of trientine used in the model is derived from discontinuation data from a retrospective cohort analysis of mainly adult patients with Wilson disease.[5] This study comprises the largest body of evidence for the use of trientine in Wilson disease. Although clinical evidence is extremely limited and randomized studies do not exist, trientine has been used worldwide for patients with Wilson disease since the 1960s. According to the clinical experts consulted by CADTH, patients who are able to tolerate chelation therapy — either DPA or trientine — benefit. Because of

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. zinc alone ($/QALY)
Zinc alone	163,367	Reference	16.55	Reference	Reference
Zinc followed by trientine	485,416	322,049	22.41	5.86	54,967

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[2]

ethical considerations (i.e., untreated Wilson disease is typically fatal or requires liver transplantation), it is unlikely that high-quality clinical evidence from a randomized controlled trial comparing trientine to placebo will ever be gathered.

  - CADTH was unable to compensate for this limitation in its reanalysis. CADTH noted that changing the extrapolation used to model trientine discontinuation (and thus, efficacy) did not have a substantial impact on the model's results because the model assumes that if a patient ceases to benefit from trientine, or if trientine is ineffective, then the patient would discontinue after a maximum of 6 additional months. Given that the model assumes substantial health gains in the patients who do benefit, this compensates for the 6-month cost in the patients who do not.

- **The proportion of patients with ALD and liver transplantation is uncertain:** The main benefit of trientine in the sponsor's model is the offsetting of the costs and health consequences associated with ALD and the subsequent need for liver transplantation . The sponsor assumes that preventing hepatic worsening will also prevent progression to ALD. The experts consulted by CADTH agreed that the successful treatment of Wilson disease prevents such hepatic consequences; however, both the magnitude of the risk of ALD and the probability of receiving a transplant or dying were perceived as highly uncertain. The sponsor assumed that patients in the WWD state would have a 5.73% chance per cycle of progressing to ALD. This assumption was based solely on evidence from older patients with cirrhosis, 51% of whom had alcoholic cirrhosis. This assumption led to 100% of patients in the no-treatment group developing ALD within their lifetime. The clinical experts consulted by CADTH considered this to be too high for patients with Wilson disease — who are generally younger and healthier than those in the source study — and suggested that an assumption of 75% progressing to ALD over their lifetimes would be plausible. Modelled patients in the ALD state then had a 10.34% chance of dying per 6-month cycle, based on the same evidence, and a 3.97% chance per cycle of undergoing liver transplantation. In contrast, of the 4 patients in Weiss et al. (2013) who discontinued trientine therapy after DPA, 3 received liver transplants[5]; no deaths were reported. The Canadian Institute for Health Information reported that 464 liver transplantations were performed in 2017, while a total of 64 patients died while waiting for a liver transplant (12%) (these figures are not specific to Wilson disease).[17] The clinical experts consulted by CADTH estimated that approximately 4% of patients with Wilson disease with ALD might die per year (2.02% per cycle), and that 3 times as many would receive a liver transplant.
  - CADTH exploratory reanalyses assumed that over their lifetimes, 75% of patients with WWD progressed to ALD if untreated by reducing the rate at which all patients with WWD progressed to ALD to 1.15% per cycle when combined with other reanalyses, given that the other changes to the CADTH reanalyses affected this rate. CADTH notes this rate would be different if combined with the sponsor's base-case assumptions. CADTH also assumed 4% of patients with ALD would die per year (2.02% per cycle) and that 12% of patients with ALD would undergo liver transplantation per year (6.19% per cycle).
- **The modelled population is not consistent with the Health Canada indication or reimbursement request:** The sponsor's model assumes that all patients who fail on DPA due to intolerance or lack of efficacy would take zinc before trientine. This treatment paradigm models trientine as a third-line therapy for Wilson disease rather than a second-line therapy following DPA, as indicated in the product monograph and reimbursement request. The clinical experts consulted by CADTH did not agree that the approximately 30% of patients who cannot tolerate DPA should be trialled on zinc before switching to trientine. According to the experts consulted by CADTH, patients with Wilson disease require

chelation therapy (i.e., DPA or trientine) except in cases where the disease is asymptomatic or where the copper burden is already low. Additionally, the efficacy of trientine in the model is derived from patients studied in Weiss et al. (2013) who received trientine after DPA; these patients did not receive 6 months of zinc in between chelating therapies. Thus, the efficacy of the treatment paradigm proposed by the sponsor is unknown. Finally, the sponsor's model assumes that all patients who have discontinued treatment will immediately experience worsening symptoms without treatment, but this assumption is not consistent with the opinion of the clinical experts consulted by CADTH. DPA, in particular, is most frequently discontinued due to AEs or intolerability; thus, patients may not experience worsening symptoms for some time after withdrawal.[5]

    - CADTH removed treatment with zinc therapy from the model in its exploratory reanalyses, assuming that all patients started on trientine in the SWD health state or on no therapy in the WWD state.
    - A scenario analysis was conducted based on input from the clinical expert consulted by CADTH that assumed that 33% of patients on no therapy after DPA discontinuation worsen within 2 years, 70% worsen by 5 years, and 100% worsen by 10 years. Due to uncertainty in the proportion of patients with stable symptoms at each time point — and the appropriate way to model the time between them — this analysis was not considered robust enough to include in the combined reanalysis.
- **The model does not account for neurologic symptoms:** The sponsor's model considers only hepatic symptoms associated with Wilson disease, assigning costs and quality of life based on hepatic health states and outcomes. However, the accumulation of copper associated with unstable Wilson disease often results in neurologic and psychiatric symptoms. Approximately 24% of patients in the Weiss et al. (2013) study had an initial presentation of neurologic symptoms, and another 20% presented with both hepatic and neurologic symptoms.[5] The clinical experts consulted by CADTH advised that untreated, the neurologic and psychological manifestations of Wilson disease will progress to irreversible impairment, with potentially profound impacts on quality of life as well as on the medical costs associated with psychiatric and long-term care.
    - CADTH was unable to adjust for this limitation in its reanalyses. If the model was capable of representing the effects of trientine compared to no treatment on neurologic outcomes, the ICER associated with trientine could be lower than reported in the current analyses, given the evidence that, like hepatic outcomes, neurologic outcomes could be better for patients receiving trientine.
- **The model structure does not reflect current practice:** The sponsor's model does not reflect the complexity of the treatment or the natural history of Wilson disease. In the model, patients start treatment with zinc or trientine and either respond and tolerate it or are unresponsive or intolerant to it. Patients may then discontinue treatment forever, in which case they are left with lifelong hepatic consequences. All patients remaining on therapy are fully adherent; thus, they gain the full benefit of treatment. The clinical experts consulted by CADTH indicated that, in practice, treatment is likely to be iterative, with some patients fully adherent but others discontinuing treatment and restarting once symptoms appear or worsen. Additionally, some responsive patients with minor symptoms may successfully transition to zinc for maintenance therapy after chelation.[18] Given the young age at which most patients with Wilson disease are diagnosed — often in adolescence or early adulthood — and the side effects and difficult-to-maintain regimens and dietary restrictions associated with treatment, nonadherence is particularly likely.[18,19] Additionally, the clinical experts consulted by CADTH indicated that patients with Wilson disease would never be left untreated. A model capable of representing time spent iteratively on and

off treatments, and the increased risks associated with a lack of adherence, may have been more reflective of real-world experience. However, because Wilson disease is a rare condition, the evidence necessary to inform such a model is lacking.

  - CADTH was unable to adjust for this limitation in reanalysis.

- **The impacts on costs and utilities do not change over time:** In the model, if a patient receives a liver transplant, their costs are higher by $27,293 every 6 months for the remainder of their life. This incremental cost may include costs related to liver transplantation as well as general health care costs. General health care costs outside of monitoring are not included in the model for patients in other health states; therefore, the incremental cost of post-liver transplantation may be overestimated. Additionally, as the patient gets older, the incremental costs associated with having received a liver transplant decades prior may also decrease. The sponsor also assumes that utility values remain static over time when those of the general population decrease as people age.[20]
  - CADTH reanalyses incorporated a utility modifier based on Guertin et al. (2018) to all health states to adjust for changes in health-related quality of life as patients age.[20] In general, utilities were higher in patients under 50 years of age compared to the sponsor's analyses, and lower in patients over 50 years of age. The sponsor may have overestimated the cost savings associated with the avoidance of a liver transplantation. A scenario analysis was conducted that reduced annual post-liver transplantation costs by 50% to assess the impact of this value.
- **The health state utility values are uncertain:** For the SWD health state utility (0.838), the sponsor used the average of the 6-month and 12-month utilities measured by Visual Analogue Scale reported in the 2019 study by Weiss et al. of patients who were using trientine after discontinuing DPA.[4] Because health utility data were not available specific to Wilson disease for patients with WWD, ALD, or who had undergone a liver transplantation, utilities from a utility study in Canadian CHC patients were used as a proxy, from patients with mild to moderate CHC (0.751), decompensated cirrhosis (0.602), and post-liver transplantation (0.651), respectively.[11] In the absence of direct evidence in a Wilson disease population, it is necessary to extrapolate from another disease; however, CADTH noted that this study produced a wide variety of utility estimates associated with quality of life in CHC, making the appropriate choices to use for proxies in Wilson disease even more uncertain.
  - CADTH performed a scenario analysis that used the highest and lowest utility estimates from the same utility study for mild to moderate CHC, decompensated cirrhosis, and post-transplantation as proxies for WWD symptoms, ALD, and post-transplantation, respectively.
- **The modelled population was too old at baseline in comparison with the population likely to initiate treatment with trientine:** The sponsor's model assumed a mean patient age of 42 years when entering the model, based on the mean baseline age of patients in a 2019 prospective study by Weiss[4] et al. on the safety and efficacy of trientine in Wilson disease in patients withdrawn from DPA. However, most patients are diagnosed with Wilson disease between 5 years and 35 years of age, often in adolescence, and the clinical experts consulted by CADTH did not consider it reasonable to assume that it would take 7 years to 37 years to determine whether a patient would be able to tolerate treatment with DPA. The mean age at diagnosis reported in Weiss et al. (2013) was 17 years or 19 years,[5] depending on the initial treatment group. Given that some delay is necessary to account for at least 1 trial of DPA therapy, CADTH considered the sponsor's scenario analysis with a mean starting age of 20 to be a more appropriate assumption. Given the variation in the age at diagnosis seen in clinical practice, CADTH also considered it appropriate to model the starting age probabilistically.

- CADTH assumed a mean starting age of 20 years in its reanalyses.

- **The mean trientine dose is uncertain**: The recommended dose of trientine for adults is 750 mg daily in divided doses, which may be increased to a maximum of 2,000 mg daily. The recommended pediatric dose (for ages 5 years to 17 years) is 500 mg daily in divided doses, with a maximum dose of 1,500 mg daily for children aged 12 years and under.[1] The sponsor's assumption of a mean dose of 1,000 mg per day is plausible, but uncertain. In Weiss et al. (2019), which was a prospective safety and efficacy study of patients using trientine after withdrawing from DPA, the mean daily reported dose was 1,377.6 mg. Because the mean age of patients in this study was 49 years, the study likely contains a higher proportion of adults than the Canadian population of Wilson disease patients; thus, this dose may be higher than what would be used in the overall population, which would be treated with trientine. Nevertheless, the model is sensitive to the mean dose assumed, and the mean dose that will be used in clinical practice is uncertain.
  - CADTH performed a scenario analysis increasing the mean daily dose to 1,378 mg from 1,000 mg.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

CADTH Reanalyses of the Economic Evaluation

Exploratory Results

Due to limitations in the body of clinical and economic evidence regarding the use of trientine for the treatment of Wilson disease, as well as limitations in the model structure, CADTH could not determine a base-case reanalysis. Instead, CADTH conducted a series of reanalyses exploring areas of uncertainty in the sponsor's model and combined them into a merged exploratory reanalysis (Table 5).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Successful liver transplantations resolve Wilson disease symptoms.	Acceptable. While the neurologic effects of uncontrolled Wilson disease would not be reversed, a successful liver transplantation would prevent further accumulation of copper; thus, hepatic symptoms should resolve and further neurologic damage would not occur.
Gender proportions are the same as for patients who received trientine therapy in Weiss et al. (2019).	Acceptable. The sponsor based the gender proportions of patients in the model on the proportion of women who received trientine therapy in Weiss et al. (2019). While the generalizability of this proportion to the Canadian population of patients with Wilson disease is uncertain, the assumption does not have a significant impact on model results.
Disutility is not applied for liver transplantation surgery.	Inappropriate. While the sponsor considered the impact of ALD and being post-liver transplantation on a patient's quality of life, no disutility was applied for patients undergoing the actual process of liver transplantation. However, given the relative transience of this event, it is unlikely that including it would substantially lower the ICER.

ALD = advanced liver disease; ICER = incremental cost-effectiveness ratio.

Most of the changes made in the exploratory analyses had only a minimal impact on the ICER associated with trientine for the treatment of Wilson disease after intolerance or lack of response to DPA. This was because changes in the assumptions had similar impacts on the incremental costs and QALYs (Table 6). The exploratory change to the rate at which patients with worsening symptoms progress to ALD had the largest impact relative to the sponsor's base case, which — when combined with other exploratory analyses — resulted in trientine being associated with $694,602 in incremental costs and 4.73 incremental QALYs, for a possible ICER of $146,927 per QALY gained.

Scenario Analysis Results

- Scenario analyses were also conducted using the CADTH combined exploratory analysis to investigate the impacts of: assuming that patients do not automatically worsen when discontinuing DPA; reducing the cost savings associated with post-liver transplantation care; considering alternate health state utility values; and increasing the mean daily dose of trientine to match that reported in Weiss et al. (2019).[4] The assumption that patients would not automatically worsen upon discontinuation of DPA increased the ICER to $295,045 per QALY, while halving the costs associated with post-liver transplantation care was associated with an ICER of just over $176,574 per QALY. The model was sensitive to the use of the highest and lowest indirect utility values reported for mild to moderate CHC, decompensated cirrhosis, and being post-liver transplantation (in Saeed [2020]); these values were used as proxies for the worsening of Wilson disease symptoms, ALD, and being post-liver transplantation. When the highest figures for these utilities were used, the ICER increased to $383,597 per QALY; using the lowest figures decreased the ICER to $98,807 per QALY. Finally, assuming a mean daily dose of trientine consistent with that reported in Weiss et al. (2019) led to an ICER of $228,886 per QALY. See Table 12.
- Price reduction analyses were conducted on the sponsor's base case and the CADTH combined exploratory analysis. To be cost-effective at a willingness-to-pay threshold of $50,000 per additional QALY when compared to no treatment, the cost of trientine would

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Zinc removed	Patients receive zinc + trientine or zinc + no treatment	Patients receive trientine or no treatment
2. Starting age	42 years	20 years
3. 6-month probability progression to ALD	5.73%	1.15%
4. 6-month probability of death with ALD	10.34%	2.02%
5. 6-month probability of LT with ALD	3.97%	6.19%
6. Utilities change with age	Utilities do not change with age	Utilities change with age proportional to those reported in Guertin 2018[a]
CADTH base case	NA	1 through 6

ALD = advanced liver disease; LT = liver transplantation; NA = not applicable.

[a]Guertin 2018.[20]

need to be reduced by approximately 7% under the sponsor's base-case assumptions, and by 46.5% under CADTH's exploratory assumptions. See Table 7.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	Zinc, then no treatment	163,367	16.55	Reference
	Zinc, then trientine	485,416	22.41	54,967
CADTH reanalysis 1: zinc removed	No treatment	391,112	11.35	Reference
	Trientine	965,700	24.64	43,235
CADTH reanalysis 2: starting age 20	Zinc, then no treatment	255,827	19.80	Reference
	Zinc, then trientine	652,127	28.19	47,265
CADTH reanalysis 3: progression to ALD	Zinc, then no treatment	110,158	21.05	Reference
	Zinc, then trientine	554,960	24.10	145,798
CADTH reanalysis 4: probability of death with ALD	Zinc, then no treatment	313,023	19.01	Reference
	Zinc, then trientine	543,957	23.35	53,168
CADTH reanalysis 5: probability LT with ALD	Zinc, then no treatment	199,508	16.81	Reference
	Zinc, then trientine	499,390	22.51	52,585
CADTH reanalysis 6: utilities decrease with age	Zinc, then no treatment	163,845	8.14	Reference
	Zinc, then trientine	488,997	14.90	48,113
CADTH combined exploratory analysis (1 through 6)	No treatment	528,132	33.94	
	Trientine	1,222,734	38.10	146,927

ALD = advanced liver disease; ICER = incremental cost-effectiveness ratio; LT = liver transplantation; QALY = quality-adjusted life-year.
Note: Probabilistic results are reported for the sponsor's base case and CADTH"s combined exploratory analysis.

Table 7: CADTH Price Reduction Analyses

	ICERs for trientine vs. no treatment	
Price reduction analysis	Sponsor base case ($)	CADTH exploratory reanalysis ($)
No price reduction	54,967	146,927
10%	**47,531**	126,014
20%	40,095	105,101
30%	32,659	84,188
40%	25,223	63,275
50%	17,787	**42,362**

ICER = incremental cost-effectiveness ratio; vs. = versus.

Issues for Consideration

- An additional product, MAR-Trientine, was recently approved by Health Canada[21] and received a positive listing recommendation with conditions from the CADTH Canadian Drug Expert Committee.[22] Due to differences in the structure and inputs of the models, it is difficult to directly compare the results of the model discussed in this report with the model from the MAR-Trientine submission. Because the clinical safety and effectiveness of the 2 brands are presumably the same, and the submitted prices were the same, any conclusion regarding the cost-effectiveness of 1 product would be the same for the other.
- MAR-Trientine is not yet regularly reimbursed. However, should it be reimbursed, its relative price may influence the cost-effectiveness of Waymade-Trientine at the submitted price. According to IQVIA Pharmastat data from the first and second quarters of 2021,[23] some MAR-Trientine claims have been publicly reimbursed at a reported average cost per unit ranging from $6.59 to $12.67 per 250 mg capsule, depending on the jurisdiction and quarter.[23]
- Unlike MAR-Trientine,[21] Waymade-Trientine requires refrigeration.[1] This may be less convenient for patients. According to the experts consulted by CADTH, it could result in lower adherence to therapy in some.
- Prior to the approval of trientine products in Canada, trientine was not available in Canada. Patients requiring treatment with trientine accessed it through the Health Canada SAP. Patient group input indicated that this process was burdensome and caused delays in access. Additionally, since the approval of trientine products, access is no longer available through the SAP. This has led some patients to report administrative burdens in accessing the products through private insurance, as well as delays and/or denials of coverage. Because trientine was previously reimbursed through the SAP, a comparison of the $20 per 250 mg capsule cost in this submission to the confidential price previously paid through the SAP may be appropriate.

Overall Conclusions

The clinical evidence regarding the use of trientine for the treatment of Wilson disease is associated with limitations due to the lack of randomized controlled trials or large observational studies. Despite this, trientine has been used for decades internationally and in Canadian patients who have received it through the SAP. For patients who fail on or cannot tolerate DPA, there are currently no alternative chelation treatments other than trientine. According to experts consulted for this review, untreated Wilson disease will generally progress to irreversible and likely fatal hepatic and/or neurologic harm.

Due to the absence of evidence, CADTH was unable to produce a reliable base-case analysis. As an exploratory analysis, CADTH removed zinc from the treatment paradigm to align with the indicated Health Canada population, 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 with ALD die, and increased the proportion of patients with ALD who receive a liver transplant. In this exploratory analysis, the ICER associated with the use of trientine in patients with Wilson disease who do not respond to or cannot tolerate DPA was $146,927 per QALY at the submitted price of $20 per 250 mg capsule. At this ICER, a 46.5% price reduction would be required to achieve an ICER of less than $50,000 per QALY. Crucially, this analysis assumes that in the absence of trientine, there are no viable treatment alternatives available to patients who currently fail on DPA, and that patients experience worsening symptoms immediately upon discontinuing DPA. However, the majority of patients who are left untreated will experience acute liver failure, resulting in significant QALY losses

under even the most conservative scenarios explored by CADTH. Annual treatment costs with trientine are high — up to $58,400 per patient — and lifelong, due to the chronic nature of the condition. Coupled with the absence of reliable clinical evidence, this leaves the assessment of cost-effectiveness uncertain and heavily reliant on expert opinion.

CADTH was unable to adjust for other limitations, including the paucity of clinical and economic evidence, the exclusion of neurologic symptoms in the model, and the assumption of 100% adherence among a young population on a treatment regimen that is difficult to tolerate. The exclusion of these considerations has an uncertain impact on the overall ICER. Some exclusions would make trientine more cost-effective (i.e., the consideration of neurologic benefit), while others would make it less cost-effective (i.e., adherence). It is important to note that the evidence to support these additions would be reliant on assumptions and expert opinion.

CADTH explored uncertainties related to the following: the assumption that patients worsen immediately upon discontinuing DPA; the cost of post-liver transplantation care; the health utilities associated with hepatic worsening; and the mean daily dose of trientine. The ICER ranged from $98,807 to $383,597 per QALY in these analyses. This further highlights the uncertainty and need to rely on expert opinion to inform cost-effectiveness.

CADTH has previously reviewed another generic trientine product at the same submitted price. The primary difference between the 2 products is that the Waymade product requires refrigeration, while the other (MAR-Trientine) does not. Due to differences in the structures and inputs of the models, it is difficult to directly compare the results of the current model with the model from the previous trientine submission. Given that the clinical safety and effectiveness of the 2 brands are presumably the same, and the submitted prices were the same, any conclusion regarding the cost-effectiveness of 1 product would be expected to hold for the other.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Wilson Disease

Treatment	Strength/ concentration	Form	Price	Recommended dosage	Daily cost	Annual cost[a]
Trientine (Waymade-Trientine)	250 mg	Capsules	$20.0000[a]	Adult: 750 mg in 2 to 4 divided doses, may increase to a maximum of 2,000 mg if required Pediatric (5 to 17): 500 mg in 2 to 4 divided doses, may increase to a maximum of 1,500 mg for patients 12 and under if required[b]	Adult: $60.00 to $160.00 Adolescent (13 to 17): $40.00 to $160.00 Child (5 to 12): $40.00 to $120.00	Adult: $21,900 to $58,400 Adolescent (13 to 17): $14,600 to $58,400 Child (5 to 12): $14,600 to $43,800
Other trientine products						
Trientine (MAR-Trientine)	250 mg	Capsules	$20.0000[c]	Adult: 750 mg in 2 to 4 divided doses, may increase to a maximum of 2,000 mg if required Pediatric (5 to 17): 500 mg in 2 to 4 divided doses, may increase to a maximum of 1,500 mg for patients 12 and under if required[b]	Adult: $60.00 to $160.00 Adolescent (13 to 17): $40.00 to $160.00 Child (5 to 12): $40.00 to $120.00	Adult: $21,900 to $58,400 Adolescent (13 to 17): $14,600 to $58,400 Child (5 to 12): $14,600 to $43,800
Other chelators						
D-penicillamine (Cuprimine)	250 mg	Capsules	3.9649	Optimal dosage determined by measurement of copper excretion and the determination of free copper in the serum. A dose between 0.75 and 1.5g. It is seldom necessary to exceed 2g per day[b]	$11.89 to $31.72	$4,342 to $11,578

Treatment	Strength/ concentration	Form	Price	Recommended dosage	Daily cost	Annual cost[a]
Zinc supplementation						
Zinc gluconate (over-the-counter brands)	10 mg 25 mg 50 mg Elemental zinc	Tablets	0.0465[d] 0.0875[d] 0.0509[d]	50 mg 2 to 3 times daily[e]	$0.18 to $0.26	$64 to $96

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2021), unless otherwise indicated, and do not include dispensing fees.

[a]Sponsor's submitted price.[2]

[b]Dosing as per product monographs. According the 2008 American Association for the Study of Liver Diseases Practice Guideline Diagnosis and Treatment of Wilson Disease, both d-penicillamine and trientine are dosed by weight, with a maximum dose of 20 mg/kg, reducing by 25% when clinically stable.[18]

[c]CADTH Draft Recommendation: MAR-Trientine.[22]

[d]IQVIA Delta PA AQPP prices (accessed September 2021).[24] Zinc gluconate tablets are over-the-counter products and not reimbursed by public plans.

[e]Minimum and usual dose as outlined in the 2008 American Association for the Study of Liver Diseases Practice Guideline.[18]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

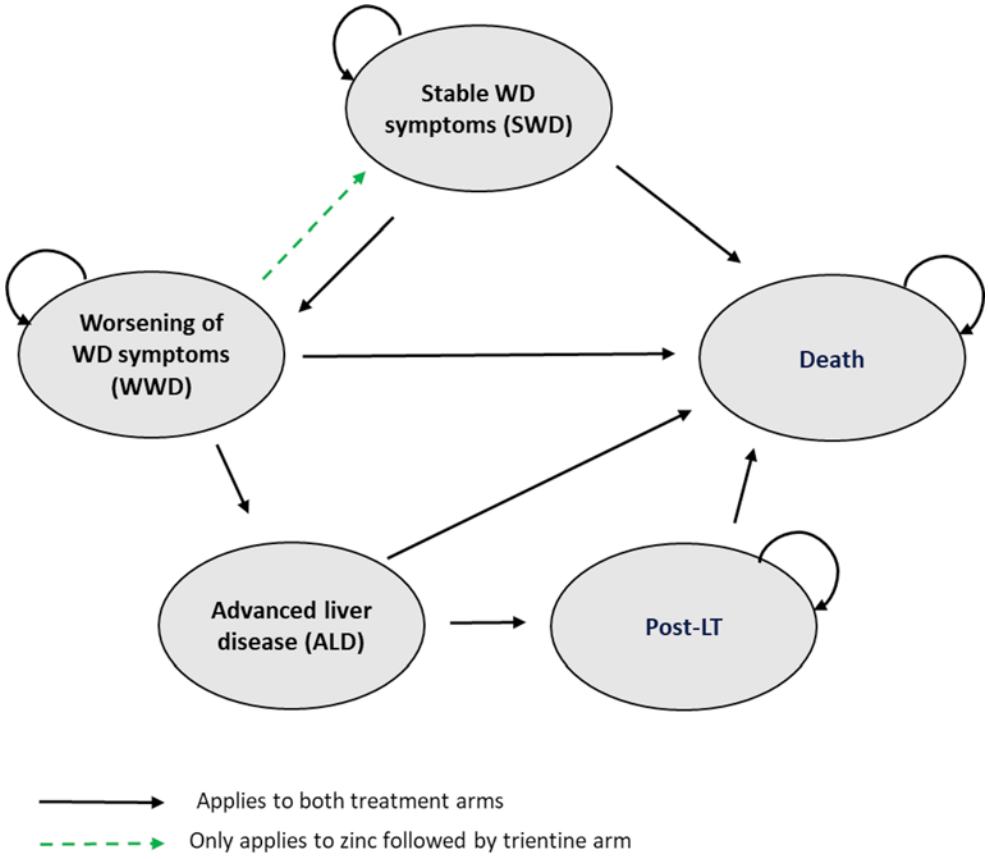
Table 9: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	The population modelled is third-line therapy after intolerance to d-penicillamine and zinc, rather than second-line therapy after intolerance to d-penicillamine as indicated. Patients are not likely to ever be left untreated in clinical practice.
Model has been adequately programmed and has sufficient face validity	Yes	The economic model is transparently laid out. In the absence of evidence, face validity is uncertain.
Model structure is adequate for decision problem	No	The model is insufficiently structured to adequately reflect the complexity of the condition and treatment paradigm. As a Markov model, it could have been structured to allow the impact of adherence and treatment cycling to be explored but was not. The neurological effects of Wilson disease were not adequately incorporated.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	No	The model lacks the ability to assess uncertainty related to long-term treatment, in particular, issues with adherence.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	No comment.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

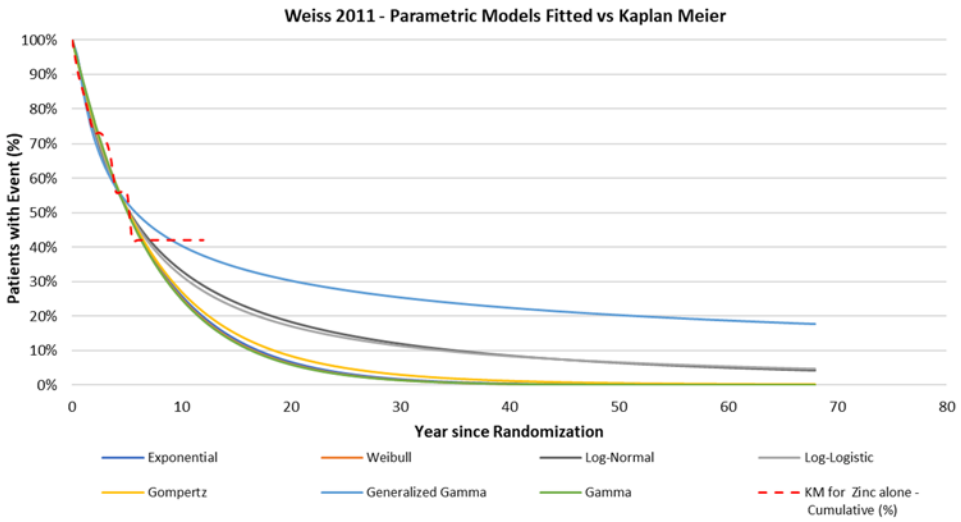
Figure 1: Model Structure



LT = liver transplantation; WD = Wilson disease.

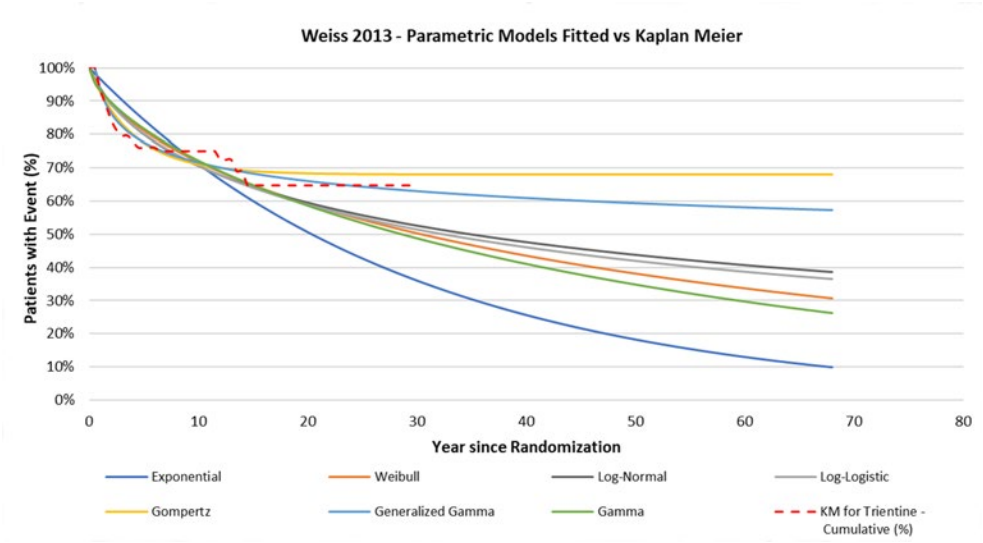
Source: Figure 2 in sponsor's pharmacoeconomic submission.[2]

Figure 2: Parametric Extrapolation Models of Time to Discontinuation for Zinc Therapy



KM = Kaplan Meier (time to discontinuation event).
Source: Submitted pharmacoeconomic model[2]

Figure 3: Parametric Extrapolation Models of Time to Discontinuation for Trientine Therapy



KM = Kaplan Meier (time to discontinuation event).
Source: Submitted pharmacoeconomic model[2]

Detailed Results of the Sponsor's Base Case

Table 10: Disaggregated Summary of the Sponsor's Economic Evaluation Results

Parameter	Zinc + Trientine	Zinc alone	Incremental
Discounted LYs			
Total	27.58	21.42	6.16
Stable WD	23.39	12.15	11.25
Worsening of WD symptoms	2.67	5.41	-2.74
Advanced liver disease	0.99	2.32	-2.74
Post-liver transplant	0.53	1.54	-1.01
Discounted QALYs			
Total	22.41	16.55	5.86
Stable WD	19.62	10.19	9.43
Worsening of WD symptoms	2.00	4.06	-2.06
Advanced liver disease	0.60	1.40	-0.80
Post-liver transplant	0.35	1.01	-0.66
Disutility associated with treatment related AEs	0.16	0.11	0.05
Utility generated within trial period	9.92	8.94	0.98
Utility generated after trial period	12.49	7.60	4.89
Discounted costs ($)			
Total	485,416	163,367	322,049
Drug acquisition	406,369	0	406,369
Medical costs	79,030	163,312	-84,283
Costs associated with regular monitoring for WD	19,433	10,092	9,341
Costs associated with monitoring for hepatic manifestations	8,346	16,938	-8,592
Costs associated with hepatic complications	51,251	136,215	-84,964
Adverse events	18	55	-37
ICER ($/LY)	52,277		
ICER ($/QALY)	54,967		

ICER = incremental cost-effectiveness ratio; LY= life-year; QALY = quality-adjusted life-year; WD = Wilson's disease.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Table 11: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Trientine	No treatment	Incremental
Discounted LYs			
Total	38.10	33.94	4.16
Stable WD	22.75	0	22.75
Worsening of WD symptoms	11.22	23.84	-12.62
Advanced liver disease	1.62	3.56	-12.62
Post-liver transplant	2.52	6.55	-4.03
Discounted QALYs			
Total	42.23	37.51	4.73
Stable WD	29.80	0	29.80
Worsening of WD symptoms	10.94	32.35	-21.41
Advanced liver disease	0.84	2.77	-3.72
Post-liver transplant	0.72	2.39	-1.66
Disutility associated with treatment related AEs	0.06	0	0.06
Utility generated within trial period	17.32	15.59	1.73
Utility generated after trial period	24.83	21.87	2.96
Discounted costs ($)			
Total	1,222,734	528,132	694,602
Drug acquisition	987,377	0	987,377
Medical costs	235,340	528,077	-292,737
Costs associated with regular monitoring for WD	19,051	0	19,051
Costs associated with monitoring for hepatic manifestations	35,088	74,564	--39,476
Costs associated with hepatic complications	181,200	452,735	-271,534
Adverse events	18	55	-37
ICER ($/LY)	167,028		
ICER ($/QALY)	146,927		

AE = adverse events; ICER = incremental cost-effectiveness ratio; LY= life-year; QALY = quality-adjusted life-year; WD = Wilson's disease.

Scenario Analyses

As the CADTH combined exploratory analysis remains uncertain, a series of scenario analyses were conducted. Results of these analyses can be found in Table 12.

A) Patients discontinuing DPA and receiving no further treatment were not assumed to immediately have worsening hepatic symptoms. Instead, a curve was constructed based on clinical expert input such that 33% had worsened by 2 years, 70% had worsened by 5 years, and everyone had worsened by 10 years.

B) Post-liver transplant costs were reduced by 50% to account for potential waning of costs over time and analyze the impact this variable has on the results.

C) The highest indirect utilities reported by Saeed 2020[11] for mild/moderate CHC (0.829), decompensated cirrhosis (0.708), and post-liver-transplant (0.75) health states were used as proxies for the worsening hepatic conditions, ALD, and post-liver-transplant health states in Wilson disease.

D) The lowest utilities reported by Saeed 2020[11] for mild/moderate CHC (0.690), decompensated cirrhosis (0.460), and post-liver-transplant (0.570) health states were used as proxies for the worsening hepatic conditions, ALD, and post-liver-transplant health states in Wilson disease.

E) The average dose of trientine was increased from 1,000 mg to 1,378 mg daily, to match the mean dose reported in Weiss 2019,[4] a prospective study of patients who had discontinued DPA.

Table 12: Summary of CADTH Scenario Analysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	Zinc then no treatment	163,367	16.55	Ref.
	Zinc then trientine	485,416	22.41	54,967
CADTH Combined Exploratory Reanalysis	No treatment	528,132	33.94	
	Trientine	1,222,734	38.10	146,927
CADTH Scenario A: WWD develops over time post-DPA	No treatment	455,328	39.47	Ref.
	Trientine	1,223,199	42.07	236,672
CADTH Scenario B: reduced post-transplant costs by 50%	No treatment	347,703	37.62	Ref.
	Trientine	1,158,503	42.21	176,574
CADTH Scenario C: higher alternate utilities	No treatment	526,834	42.10	Ref.
	Trientine	1,228,743	43.93	383,597
CADTH Scenario D: lower alternate utilities	No treatment	527,726	33.87	Ref.
	Trientine	1,231,432	41.00	98,807
CADTH Scenario E: higher trientine dose	No treatment	585,804	37.28	Ref.
	Trientine	1,603,950	41.99	228,886

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; WWD = worsening Wilson disease; Ref. = reference.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 13: Summary of Key Take-Aways

Key Take-aways of the BIA
• 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 unable to account for the offsetting of medications required for the hepatic and neurological 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.

Summary of Sponsor's BIA

In the sponsor-submitted BIA,[25] the sponsor assessed the reimbursement of trientine for patients with Wilson disease who are intolerant to DPA compared to no treatment. The BIA was conducted from a Canadian public drug payer perspective over a 3-year time horizon using a claims-based approach and included only drug acquisition costs.

Data for the model was obtained from various sources including: Statistics Canada, the Canadian Institute for Health Information, the scientific literature, and expert opinion. Key inputs to the BIA are documented in Table 15.

The sponsor's submission included the following key assumptions:

- Patients who have been prescribed and failed treatment with DPA are symptomatic in the same proportions as the overall population of patients with Wilson disease.
- Patients with Wilson disease are eligible for public coverage in the same proportions as the general population.
- Downstream therapies such as those associated with liver transplantation will not be affected by the reimbursement of trientine.
- Other brands of trientine will not already be reimbursed when Waymade-Trientine reimbursement begins.

Table 14: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as Year 1 / Year 2 / Year 3 if appropriate)
Target population	
Population of included jurisdictions	30,114,315 / 30,473,610 / 30,832,169[a]
Prevalence of WD	0.0033[b]

Parameter	Sponsor's estimate (reported as Year 1 / Year 2 / Year 3 if appropriate)
Proportion of WD patients intolerant to DPA	30%[b]
Proportion of WD patients who are symptomatic	70%[c]
Proportion WD patients aged <65 years	97.8%[d]
Proportion of population aged <65 years covered by public plans	28.2%[e,f]
Proportion WD patients aged 65+ years	2.2%[d]
Proportion of population aged 65+ years covered by public plans	90.4%[e]
Number of patients eligible for drug under review	62 / 62 / 63
Treatment adherence	74.1%[g]
Market Uptake – Reference Scenario (3 years)	
No treatment	100%
Market Uptake – New Drug Scenario (3 years)	
No treatment Trientine	0% 100%
Cost of treatment (per patient per year)	
Trientine (1,000 mg daily assumed)	$29,200

DPA = d=penicillamine; WD = Wilson disease.

[a]Statistics Canada projected population.[26]

[b]Roberts et al., 2008[18]

[c]Moores et al. 2012[27]

[d]Choe et al. 2020[28]

[e]CIHI 2020[29]

[f]Conference Board of Canada 2017[30]

[g]Maselbas et al. 2019[31]

Summary of the Sponsor's BIA Results

Results of the sponsor's base-case BIA suggest that the yearly incremental expenditures associated with the reimbursement of trientine, including dispensing fees and markup, for patients intolerant to DPA were expected to be $1,266,398 in Year 1, $1,281,384 in Year 2, and $1,296,362 in Year 3, for a 3-year cumulative total of $3,844,144. When dispensing fees and markups are excluded, the sponsor's model reports an incremental budget impact of $399,349 in Year 1, $479,219 in Year 2, and $575,062 in Year 3, for a 3-year cumulative total of $1,453,630. The sponsor conducted scenario analyses varying the proportion of patients aged <65 years, the mean daily dose of trientine, and the annual growth rate in the number of patients on trientine by 25%. All scenarios had 3-year cumulative totals between $1.2 and $2.6 million

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Eligible population underestimated:** The sponsor's model estimates that 70% of patients who have failed DPA therapy would be symptomatic, while 30% would be asymptomatic and thus not require treatment with trientine within the time horizon of the BIA. This assumption is based on a 2012 chart review of 48 Canadian patients with Wilson disease, 14 of whom were asymptomatic at diagnosis (29%). Of note, after diagnosis, 8 of those 14 patients were put on DPA therapy and 1 was given trientine, suggesting that many asymptomatic patients also receive chelation therapy at least to start, with the implication that those who fail to tolerate

1 chelation therapy may be placed on another. While 6 of these 9 patients had switched to zinc alone rather than remaining on a chelator by the time of chart review, an average of 11.5 years had passed since diagnosis, far longer than the time horizon of the BIA. Thus, only 5 of 48 patients did not require chelation therapy, rather than 14 of 48 as assumed by the sponsor. CADTH reviewers also note that logically, the proportion of patients who do not require chelation therapy should be filtered out from the eligible population prior to a trial of DPA therapy, rather than after, although the resulting population size is not affected in this case.

- CADTH increased the proportion of Wilson disease patients who would require chelation therapy to 89.6% (43/48), and applied this proportion before applying the proportion of patients who were intolerant to DPA rather than afterward.

- **Funding previously spent in SAP program not accounted for:** Prior to November 2020, trientine was previously available to Canadian patients though the SAP program. The sponsor's model does not account for funds previously used to acquire trientine before market authorization.
  - CADTH was unable to account for this limitation in reanalyses. The pan-Canadian (excl. Quebec) budget impact associated with reimbursing trientine through the public formularies would be lower than projected by the amount that was previously being spent to acquire trientine for patients accessing it through the SAP program.
- **Downstream medications were not considered:** Treatment with trientine reduces the number of patients with Wilson disease who require liver transplantation, see the economic evaluation. Additionally, unstable Wilson disease is associated with neurological and psychiatric consequences. Due to this, the costs associated with reimbursing trientine are expected to be partially offset by the reduced number of patients requiring anti-rejection or other medications for hepatic consequences of unstable Wilson disease as well as medications associated with the neurologic and psychiatric worsening.
  - CADTH was unable to account for this limitation in reanalyses. The budgetary impact of reimbursing trientine would be lower than projected if downstream medications avoided were included.
- **Number of Wilson disease patients eligible for public funding is underestimated:** The sponsor used the proportion of the population in each jurisdiction who are active beneficiaries of the public drug plans,[29,30] stratified by age over and under 65 years, to determine the number of patients using trientine who would be publicly reimbursed. However, due to the high annual cost of treatment, patients requiring trientine would be far more likely than the general population to require assistance to pay for their therapy. According to the Conference Board of Canada,[30] the primary reason eligible Canadians are not enrolled in a public program may be as simple as not requiring coverage or being comfortable paying their costs out-of-pocket. Neither of these explanations are likely to be applicable to patients with Wilson disease requiring trientine therapy. As such, the proportion of patients who are reimbursed by the public plans for trientine may be better represented by the proportion of the population over and under age 65 who are eligible for public coverage, rather than only those who are currently active beneficiaries.
  - In its base-case reanalysis, CADTH considered the proportion of the population who are eligible for public reimbursement to better represent the proportion of patients with Wilson disease who would seek public reimbursement for trientine.
- **Some eligible patients may not access trientine in the first year:** The sponsor uses a prevalence-based approach to estimating the number of patients with Wilson disease in Canada and the proportion of those patients who will require treatment with trientine. The sponsor then assumed that 100% of patients who will eventually require trientine therapy will receive it in the first year of its reimbursement. However, it may be that some patients who have failed or will fail DPA therapy may not access publicly reimbursed trientine in its first year, instead continuing on DPA at the same or a lower dose, or attempting a trial with zinc alone, or experiencing a lag in reimbursement access.
  - CADTH conducted a scenario analysis in which only 50% of otherwise eligible patients accessed trientine in the first year of its reimbursement, rising to 80% in Year 2 and 100% in Year 3.
- **Adherence rate is uncertain:** The sponsor assumed an adherence rate for trientine of 74% was based on a Polish study[31] which determined only 74% of Wilson disease patients were persistent with DPA or zinc therapy over a mean follow-up of 11.7 years, with a lack of persistence being defined as at least 1 reported break in therapy of more than 3 months, or 2 breaks lasting longer than 2 months over the treatment period. In the BIA model, the proportion was used to decrease the monthly cost of trientine therapy. The applicability of the 74% figure is uncertain as 1) the cost-effectiveness of trientine was modelled without considering adherence and thus the BIA is inconsistent with the cost-utility analysis if adherence is included, 2) trientine is reportedly easier to tolerate than either DPA or zinc and thus persistence data from patients using DPA or zinc may be of limited relevance to persistence with trientine, 3) the proportion of patients who take a treatment break over many years is not the same as the proportion of missed doses of a treatment over time, and 4) the extent to which missed doses effectively delay or reduce prescription renewal and thus reduce actual costs

paid by public plans is unknown. While adherence is an issue given the young age at which most patients with Wilson disease are diagnosed and the side effects and difficult-to-maintain regimens and dietary restrictions associated with treatment,[18,19] it is unclear what proportion of trientine doses should be assumed to be missed.

- For consistency with the economic evaluation and in order to be conservative, an adherence rate of 100% was assumed in the CADTH base case. A scenario analysis was also conducted where the sponsor's adherence rate of 74% was once again considered.

- **Copayments were insufficiently modelled and not appropriate in the base case:** The sponsor's model attempts to account for copayments, the amount that a patient must pay when filling a prescription reimbursed by a public drug plan. Such copayments often include a deductible, a certain dollar amount the patient must pay toward prescriptions before they are reimbursed by the plan over a certain time period, and/or a copayment, an amount the patient must pay per prescription. Deductibles and copayments are often based on income level and vary between jurisdictions and the precise plan the patient is covered under.[29] As such, a number of assumptions about patients' incomes and their plans are required in order to appropriately account for deductibles and copayments, which are unlikely to be sufficiently robust to warrant inclusion in a base case. The sponsor's model only considered deductibles in British Columbia and Alberta and assumed that patients had an average income level. CADTH did not consider this method of including copayments to be sufficient or appropriate.
  - CADTH excluded the consideration of copayments from their subsequent reanalyses. As the sponsor's model was programmed to allow such an exclusion, CADTH considered this a correction rather than a reanalysis.

CADTH Reanalyses of the BIA

CADTH revised the sponsor's base case by: removing patient copays from consideration, increasing the proportion of patients who require chelation therapy, considering the proportion of Canadians who are eligible for public reimbursement rather than those who are enrolled, and assuming 100% adherence. Table 15 outlines the parameters used by the sponsor in comparison to those used by CADTH.

Table 15: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections[a] to sponsor's base case		
1. Removal of copay	Copays included	Copays excluded
Changes to derive the CADTH base case		
1. Patients requiring chelation	70%	89.6%
2. Patients publicly reimbursed	Enrolled beneficiaries	Eligible beneficiaries
3. Adherence	74.1%	100%
CADTH base case	1 + 2 + 3	

Applying these changes increase the total 3-year budget impact of reimbursing trientine for patients with Wilson disease who are intolerant to DPA to $15,777,456 when dispensing fees and markups are included, or $14,935,472 when they are not. The results of the CADTH step-wise reanalysis is presented in summary format in Table 16 and a more detailed breakdown is presented in Table 17.

Table 16: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	3-year total
Submitted base case	$3,844,144
Corrected sponsor's base case	$4,251,202
Corrected sponsor's base case, excluding fees and markups	$4,053,422

Stepped analysis	3-year total
CADTH reanalysis 1: Patients requiring chelation	$5,440,527
CADTH reanalysis 2: Patients eligible for public reimbursement	$9,180,101
CADTH reanalysis 3: 100% adherence	$5,725,117
CADTH base case (1 through 3)	$15,777,456
CADTH base case (1 through 3), excluding fees and markups	$14,935,472

BIA = budget impact analysis.

CADTH also conducted additional scenario analyses to address remaining uncertainty:

A. Adherence was assumed to be 74.1% as presented by the sponsor.

B. 50% of otherwise eligible patients were assumed to access trientine in its first year of reimbursement, rising to 80% in Year 2 and 100% in Year 3.

C. The price of trientine was reduced by 46.5% as suggested in the economic evaluation.

Table 17: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Submitted base case	Budget impact	$0	$1,266,398	$1,281,384	$1,296,362	$3,844,144
Corrected sponsor's base case	Budget impact	$0	$1,400,542	$1,417,074	$1,433,586	$4,251,202
CADTH base case	Budget impact	$0	$5,191,012	$5,259,144	$5,327,301	$15,777,456
CADTH Scenario A: 74% adherence	Budget impact	$0	$3,865,280	$3,916,108	$3,966,956	$11,748,344
CADTH Scenario B: lag in switching to trientine	Budget impact	$0	$2,595,506	$4,207,315	$5,327,301	$12,130,122
CADTH Scenario C: 46.5% trientine price reduction	Budget impact	$0	$2,807,837	$2,844,840	$2,881,859	$8,534,536

BIA = budget impact analysis.

Note: Because the reference scenario in all analyses was $0, only the budget impact is presented.