

5.15 TRIENTINE, Tablet 150 mg (as tetrahydrochloride), Cuprior[®], Orphalan

1 Purpose of submission

- 1.1 The Category 1 submission requested Authority Required listing for trientine tetrahydrochloride (trientine 4HCl) for the treatment of patients with Wilson Disease (WD) who are intolerant of D-penicillamine/penicillamine (DPA).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with Wilson Disease intolerant to D-penicillamine/penicillamine (DPA) and with evidence of excess copper requiring chelation therapy
Intervention	Trientine tetrahydrochloride (4HCl). The recommended adult dose is between 450 mg and 975 mg per day in 2 to 4 divided doses. The recommended dose for children aged ≥ 5 years is between 225 mg and 600 mg per day in 2 to 4 divided doses.
Comparator	Best supportive care (i.e. no copper chelation)
Outcomes	Copper levels; progression to symptomatic disease; mortality
Clinical claim	Trientine 4HCl has superior efficacy relative to best supportive care (i.e. no chelation therapy) Trientine 4HCl has an inferior, albeit manageable, safety profile relative to best supportive care (i.e. no chelation therapy)

Source: Table 1-1, p13 of the submission and the draft Product Information.

2 Background

Registration status

- 2.1 Trientine 4HCl was approved for registration by the TGA on 15 July 2021 for the treatment of Wilson's Disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.
- 2.2 The TGA Delegate noted that trientine 4HCl is a different formulation and strength to the trientine dihydrochloride (2HCl) formulations that have been in clinical use for many years. The rationale for developing the 4HCl product is that the stability of the 4HCl formulation offers patients greater flexibility and convenience in terms of storing the medicine at room temperature.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TRIENTINE TETRAHYDROCHLORIDE Tablet 150 mg, 72	144	5	\$ [REDACTED]	Cuprior® Orphalan

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Episodicity:	Chronic
PBS indication:	Wilson Disease
Treatment phase:	Initial
Restriction:	<input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Treatment criteria:	Must be treated by a gastroenterologist, hepatologist or neurologist
Clinical criteria:	Patient must be intolerant to treatment with D-penicillamine AND Patient requires copper chelation therapy
Treatment phase:	Continuing
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone, Electronic
Clinical criteria:	The patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must be requiring ongoing chelation therapy by physician assessment
Prescriber Instructions:	Evidence of excess copper can be based on clinical symptoms or measured copper levels ('free' copper in the serum [referred to non-ceruloplasmin bound copper] or urinary copper excretion)

3.1 No special pricing arrangement was proposed.

3.2 The requested price of \$ [REDACTED] for 144 x 150 mg tablets was considerable, particularly given that use of trientine was first reported in the 1970's¹ and it is relatively inexpensive to manufacture². Therefore, the requested price was not likely to be related to recovery of drug development costs. The submission did not justify the high requested price for trientine 4HCl and did not claim an advantage based on the possible convenience of being able to store the medicine at room temperature (as compared to trientine 2HCl, which requires refrigeration). The Pre-Sub-Committee Response (PSCR) stated that the trientine 4HCl tablet, which is stable at room temperature, allows more convenient dosing and advantages in terms of portability, storage and ease of swallowing.

¹ Walshe JM. In Papadatos CJ and Bartsocas CS (eds), 1979: *The management of genetic disorders*; p271-280. Alan R. Liss, Inc., New York.

² Purchase R. The production of pharmaceutical grade trientine dihydrochloride for the treatment of Wilson's disease: a personal account. *UK Newsletter, Wilson's Disease Support Group* 2016; p12-14.

- 3.3 The requested restriction did not specify that patients must be 5 years or older, as stated in the TGA indication. The pre-PBAC response stated that the restriction should restrict use to in patients aged 5 years and older.
- 3.4 The proposed restriction positioned trientine 4HCl as a second-line treatment in patients intolerant to DPA. Although this aligned with the TGA indication, it was not consistent with the three available treatment guidelines developed for WD from the American Association for the Study of Liver Diseases (AASLD), the European Association of the Study of the Liver (EASL) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)³, nor was it consistent with some state-based hospital formularies, all of which considered that the initial therapy should be a chelating agent consisting of either DPA or trientine. Noting the available guidelines and the clinical evidence presented, the PBAC considered that the proposed place in therapy for trientine 4HCl should be line agnostic.
- 3.5 The Secretariat had additionally suggested that the proposed indication of ‘Wilson disease’ be re-framed to ‘copper chelation’ with the eligibility criteria further refining the patient population to that having a diagnosis of Wilson disease because this better reflected the true indication of drug treatment.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Wilson Disease (WD) is a rare autosomal recessive disorder that if left untreated results in pathological copper accumulation. The reported prevalence of WD is 0.33 per 10,000 persons with a birth prevalence of 0.22 per 10,000. The underlying cause of WD is one or more mutations in the ATP7B gene, located on chromosome 13. Over 800 different mutations have been identified, though not all are confirmed as pathogenic. The prevalence of ATP7B mutations is much higher than of WD, and it is possible that the spectrum of disease associated with ATP7B mutations is wider than is currently appreciated. The ATP7B protein mediates the binding of copper molecules to apoceruloplasmin in hepatocytes, forming ceruloplasmin that transports copper within the body while avoiding the presence of ‘free’ copper, which is toxic.
- 4.2 In patients with WD, mutations in the ATP7B gene result in a defective ATP7B protein, resulting in inadequate copper transport and thus, copper accumulation in the hepatocytes. Untreated, the disease results in hepatic fibrosis and ultimately cirrhosis, and a wide spectrum of signs and symptoms are observed including hepatic as well as neurologic or neuropsychiatric manifestations. The disease can present at any age, with the majority of patients diagnosed between 5 and 35 years. Asymptomatic

³ Saroli Pulumbo C, Schilsky ML. Clinical practice guidelines in Wilson disease. *Ann Transl Med.* 2019;7(Suppl 2):S65.doi:10.21037/atm.2018.12.53

patients are most often detected by targeted family screening. Symptoms at the time of the initial presentation, and those that evolve undetected, are usually either hepatic or neurologic/neuropsychiatric. Data specific to Australia were not provided in the submission. The PSCR noted that Miraldo 1953 reported that after initially presenting with symptoms, patients' estimated life expectancy associated with untreated WD was 4 years; whereas patients with well-managed WD will have a close to normal life expectancy (EASL, 2012; Ferenci 2019).

- 4.3 Treatment of patients with WD generally consists of two phases – 'de-coppering' using chelation treatments, assessed by 24hr urinary copper excretion (24hr UCE) - and then a maintenance phase. The length of the de-coppering phase is a matter of clinical judgement.
- 4.4 Trientine (as the tetrahydrochloride or dihydrochloride; in the USA the approved name for the dihydrochloride is trientine hydrochloride), first used in 1969, is a copper chelator that after oral intake is absorbed and has systemic action by forming stable complexes with copper that are excreted in the urine. It is less readily absorbed following oral intake compared to DPA, so it may also act through the chelation of copper in the intestinal tract, thus inhibiting absorption of dietary copper.
- 4.5 Both DPA and trientine (as dihydrochloride) have been used for many years as chelation therapy. Zinc is also a recognised treatment, mainly as an alternative to chelation for prevention of re-accumulation after de-coppering. Liver transplant is considered an alternative in patients with severe hepatic disease, and, if successful, is curative.
- 4.6 Adverse effects of DPA are common and may be severe, including sensitivity reactions, which occur soon after treatment is initiated, proteinuria and nephrotic syndrome, which can occur early or after prolonged treatment, worsening of neurological symptoms, and a wide spectrum of immune-mediated illness, including polymyositis, Goodpasture syndrome, lupus-like reactions, and skin changes. Trientine is believed to cause fewer adverse events than DPA, and although the TGA indication is for use in patients with WD who are intolerant of DPA, trientine could be used as first line treatment in some patients.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated best supportive care (BSC), consisting of ongoing monitoring for liver function, a low copper diet, vitamin E supplementation and serum copper tests, as the comparator on the grounds that no other pharmacological treatments are available for patients with WD who are intolerant of DPA. The ESC advised that BSC may also include liver transplant.

- 5.2 As described above, trientine is used in current practice for symptomatic patients in the de-coppering phase of treatment who develop adverse effects from DPA, and therefore the submission proposed BSC represents a hypothetical comparator for establishing clinical and cost effectiveness of trientine 4HCl. The evaluation commented that in the maintenance phase of treatment, and for asymptomatic patients, zinc would be an appropriate comparator. The PSCR stated that data from the CHELATE study supported the continued need for chelation therapy in the long term, and that only a small proportion of patients (13%) were reported as ever receiving zinc for the management of their WD at a mean time from diagnosis of almost 20 years. The ESC noted that zinc is recommended in the three available treatment guidelines⁴ in the maintenance phase and considered it may be used for a proportion of patients. The PSCR noted that the use of zinc in the maintenance phase in the economic model would reduce the treatment cost of trientine and thus improve the cost-effectiveness.
- 5.3 The PBAC noted that the three available treatment guidelines recommended a chelating agent, consisting of either DPA or trientine, as initial therapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that only one health care professional provided input via the Consumer Comments facility on the PBS website. The comment stated that trientine has been available to patients for several years via the special access scheme at a price which PBAC noted is much less than that requested in the submission. The health care professional did not support a PBS listing of trientine at a higher price than is currently available to hospitals.

Clinical studies/trials

- 6.3 There is an extensive body of published studies dating from the late 1960s about the use of chelating agents – both DPA and trientine in various formulations of the dihydrochloride salt - in the treatment of WD. All the published studies are observational studies, mostly retrospective case series, and are of generally poor quality. There appear to be two main groups of publications: those from authors

⁴ Saroli Pulumbo C, Schilsky ML. Clinical practice guidelines in Wilson disease. *Ann Transl Med.* 2019;7(Suppl 2):S65.doi:10.21037/atm.2018.12.53

linked to a centre in Germany (Heidelberg) and the rest; very few of the other centres have more than one or two publications.

- 6.4 A search of Clinicaltrials.gov carried out during the evaluation identified 10 registered trials and studies that are of potential relevance to the assessment of trientine.
- 6.5 The submission presented an indirect comparison of trientine 4HCl versus best supportive care, targeting the patient population who are intolerant of DPA.
- 6.6 The evidence used in the submission was a selection of the published observational studies, including some of those in a published systematic review, and one unpublished randomised trial. These studies are listed in Table 2. The basis for the selection of these studies and the exclusion of others was poorly justified in the submission.
- 6.7 Firstly, the submission referred to the bridging pharmacokinetic studies that were used to establish the equivalence, but not interchangeability, of trientine 4HCl with existing trientine dihydrochloride products. This claim has been accepted by the TGA.
- 6.8 Three observational studies were used to support the claim that trientine (mostly as dihydrochloride) was non-inferior to DPA with respect to a variety of clinical outcomes. The unpublished randomised head to head trial (CHELATE) compared trientine 4HCl to DPA in patients stabilised on DPA (that is, in the maintenance phase of treatment) and was provided as evidence of the non-inferiority of trientine (4HCl) versus DPA.
- 6.9 Five observational studies were selected to establish the benefit of chelation therapy versus best supportive care. The published meta-analysis presented a summary estimate of effect size based on four of these studies and the submission updated that analysis with data from a fifth study.

Table 2: Studies and associated reports presented in the submission

Study	Protocol title/ Publication title	Publication citation
Trientine vs. DPA		
Merle 2007	Merle, U., M. Schaefer, P. Ferenci and W. Stremmel. Clinical presentation, diagnosis and long-term outcome of Wilson's Disease: a cohort study.	<i>Gut</i> 2007; 56(1): 115-120.
Weiss 2013	Weiss, K. H., F. Thurik, D. N. Gotthardt, M. Schafer, U. Teufel, F. Wiegand, U. Merle, D. Ferenci-Foerster, A. Maieron, R. Stauber, H. Zoller, H. H. Schmidt, U. Reuner, H. Hefter, J. M. Trocetto, R. H. J. Houwen, P. Ferenci and W. Stremmel. Efficacy and safety of oral chelators in treatment of patients with Wilson disease.	<i>Clin Gastroenterol and Hepatol</i> 2013; 11(8): 1028-1035
Pfeiffenberger 2018	Pfeiffenberger, J., C. M. Lohse, D. Gotthardt, C. Rupp, M. Weiler, U. Teufel, K. H. Weiss and A. Gauss. Long-term evaluation of urinary copper excretion and non-caeruloplasmin associated copper in Wilson disease patients under medical treatment.	<i>J Inherit Metab Dis</i> 2019; 42(2): 371-380.
CHELATE	Clinical Study Report for Primary Analysis. Trientine tetrahydrochloride (TETA 4HCl) for the treatment of Wilson's disease (study number GMPO-131-002)	April 2021
Chelation vs. BSC		
Goldstein 1968	Goldstein NP, Tauxe WN, McCall JT, Randall RV, Gross JB. What Wilson's Disease and its treatment have taught us about the metabolism of copper. Observations in 27 cases.	<i>Med Clin North Am</i> 1968; 52(4): 989-1001.
Sternlieb 1968	Sternlieb I, Scheinberg IH. Prevention of Wilson's Disease in asymptomatic patients.	<i>NEJM</i> 1968; 278(7): 352-9.
Strickland 1973	Strickland GT, Frommer D, Leu ML, Pollard R, Sherlock S, Cumings JN. Wilson's Disease in the United Kingdom and Taiwan. I. General characteristics of 142 cases and prognosis. II. A genetic analysis of 88 cases.	<i>Q J Med</i> 1973; 42(167): 619-38.
Durand 2001	Durand F, Bernuau J, Giostra E, et al. Wilson's Disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine.	<i>Gut</i> 2001; 48(6): 849-52.
Scheinberg 1987	Scheinberg IH, Jaffe ME and Sternlieb I. The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson's Disease.	<i>NEJM</i> 1987;317(4): 209-213
Systematic review/meta-analysis		
Appenzeller-Herzog 2019	Appenzeller-Herzog C, Mathes T, Heeres MLS, Weiss KH et al. Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies.	<i>Liver Int</i> 2019; 39(11): 2136-2152

Source: Table 2.7, p51 of the submission.

BSC = best supportive care; DPA = D-penicillamine

6.10 The key features of the included evidence are summarised in the table below. The risk of bias was high in all the observational studies based on assessment with the ROBINS-1 and Newcastle-Ottawa instruments. In some studies the claim by the submission that patients not receiving DPA had received what would be considered BSC in today's setting was not reasonable, as given the age of the studies (1968 to 2001), what was used in those studies is not representative of current BSC. Little of the clinical evidence presented was used in the economic model, with only data from Weiss 2013 and the Appenzeller-Herzog 2019 meta-analysis used. Survival data for trientine 4HCl used in the model was sourced from another publication, Sipila 2020, which was not included in the clinical evidence presented.

Table 3: Key features of the included evidence

Trial/study ID	N	Design	Risk of bias	Patient population	Outcomes reported in submission	Use in modelled evaluation
Studies of trientine vs. DPA						
CHELATE	53	R, OL	Low	Patients with WD on maintenance treatment with DPA	Serum NCC at 36 weeks	Not used
Merle 2007	163	RR	High	Diagnosed WD patients; diagnosis using clinical, biochemical, histological and genetic evidence	Hepatic and neurologic/psychiatric symptoms Long-term treatment outcome	Not used
Weiss 2013	380	RR	High	Confirmed WD patients (diagnosis was reviewed against Leipzig score which had to be ≥ 4)	Neurologic and hepatic symptoms AEs leading to therapy discontinuation	Patient characteristics; Time to treatment discontinuation
Pfeiffenberger 2018	321	RR	High	Confirmed diagnosis of WD (Leipzig score ≥ 4)	Serum NCC 24-hour UCE	Not used
Studies of chelation vs. BSC						
Goldstein 1968	27	RR	High	Diagnosed WD patients (based on clinical signs and symptoms, biochemical parameters)	Mortality; presence/absence of symptoms	Not used
Sternlieb 1968	53	RR	High			
Strickland 1973	142	RR	High			
Durand 2001	17	RR	High			
Scheinberg, 1987	24	RR	High	Diagnosed WD patients (based on clinical signs and symptoms, biochemical parameters, family history)		
Systematic review/meta-analysis						
Appenzeller-Herzog 2019	23 studies; 2,055 patients	SR	High ^a	WD patients treated with DPA, trientine, TTM or zinc	Mortality; asymptomatic/improved	Inverse of OR for BSC survival

Source: Table 2-13, p59; Table 2-18, p66 of the submission.

AE = adverse event; BSC = best supportive care; DPA = D-penicillamine; NCC = non-ceruloplasmin bound copper concentration; OL = open label; OR = odds ratio; R = randomised; RR = retrospective review; SR = systematic review; TTM = tetrathiomolybdate; UCE = urinary copper excretion; WD = Wilson Disease

^a While the systematic review was appropriately conducted, risk of bias remains high as the included studies were all high risk of bias.

6.11 As noted above, the presented studies were selected from a number of observational studies in the published literature. The submission also referred to several other studies but did not present them in detail. It appeared that there were only two or three centres recruiting patients for studies and that many of the publications included data from the same patients. The table below summarises all the published studies that were identified during the evaluation as possibly relevant and attempts to identify the different patient cohorts that are included in the different publications. All of the most recent studies appear to come from the Heidelberg group. It is noted that the systematic review (Appenzeller-Herzog, 2019) is a meta-analysis of case series, rather than of controlled trials.

Table 4: Relationships between principal published observational studies

Reference	Centre	Period of study	N and notes
Goldstein 1968 ^a	Not reported	Not reported	27; 4/27 not treated with DPA but reason not reported
Sternlieb 1968 ^a	New York; ? others	Not reported	174; 121 were symptomatic patients whose records were adequate to determine age at onset of symptoms; 53 were asymptomatic patients
Strickland 1973 ^a	UK and Taiwan	Not reported	142 (87 UK, 55 Taiwan); 21/36 patients not treated with DPA were diagnosed retrospectively
Scheinberg 1987	New York; ? others	Not reported	11 patients stopped DPA against medical advice, did not receive trientine for unstated reasons, were (apparently) not followed up, and represented with advanced disease; 13 patients stopped DPA on medical advice and received trientine
Durand 2001 ^a	Paris, Geneva, Jerusalem	1969-1999	17 (Geneva 1, Jerusalem 2); first presentation with advanced liver disease: eligibility required symptoms < 2 months before admission, and haemolytic anaemia and "prothrombin < 50% normal" at admission
Merle 2007	Heidelberg	2000-2005	163; "either diagnosed or had a previously established diagnosis confirmed" in the period of study, so not an inception cohort; reports "side-effects" on DPA, trientine and zinc
Weiss 2011	Heidelberg and Vienna	1954-2008	288 (65 in Vienna); median follow-up 17 years, so probably includes patients reported by Merle; reports discontinuation and treatment failure of zinc, DPA and trientine treatment
Weiss 2013	Heidelberg, Dresden, Dusseldorf, Vienna, Graz, Linz, EUROWilson Registry	Not reported	405 (25 Registry); numbers per centre not reported, but probably mostly patients reported by Merle and Weiss, 2011; reports treatment outcomes and adverse effects leading to discontinuation
Pfeiffenberger 2018	Heidelberg	2003-2015	321; overlap with previous Heidelberg series unclear; only NCC and 24hr UCE reported
Weiss 2018 (Abstract)	Heidelberg, Athens, Milan, London	Not reported	77; trientine treatment following DPA withdrawal; not an inception cohort and overlap with previous Heidelberg series unclear
Weiss 2019 (Abstract)	Heidelberg	Not reported	52; continuation of Weiss, 2018, but how 52 patients were selected is not reported

Source: Compiled from publications.

DPA = D-penicillamine; NCC = non-ceruloplasmin bound copper concentration; UCE = urinary copper excretion

^a Included in Appenzeller-Herzog 2019 meta-analysis.

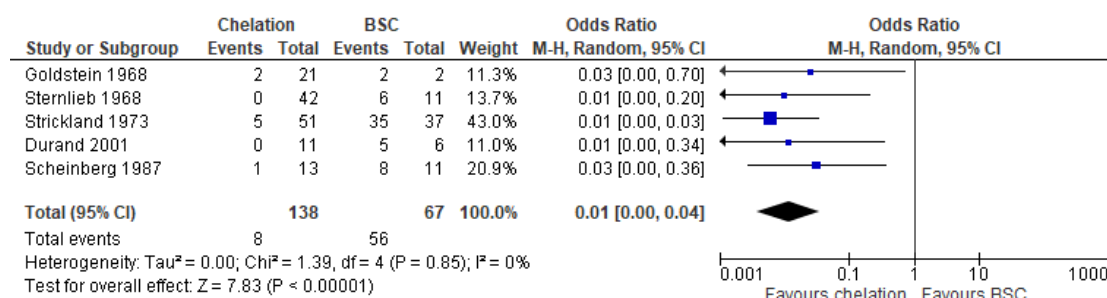
6.12 In the context of an old product and a rare disease, the lack of randomised trials for trientine was understandable. However, given the overall quality of evidence, any attempt to estimate an effect size for use as the basis of a cost-effectiveness claim, and thus a basis for setting a price, would be extremely uncertain.

6.13 The evaluators questioned whether an alternative approach to the economic evaluation would be more appropriate, such as a cost minimisation analysis versus DPA for both initial treatment and maintenance in a first line population, notwithstanding the TGA indication; or a cost-effectiveness analysis versus zinc in maintenance treatment populations. The first comparison might be adequately supported by the existing published studies despite their limitations; the second might depend more on the results of the ongoing studies. The PSCR stated that the TGA indication should not be ignored and that a cost-minimised price for trientine 4HCl versus DPA would not be commercially viable.

Comparative effectiveness

- 6.14 The observational studies comparing trientine and DPA were difficult to interpret because of inconsistent reporting and the poor quality of the studies.
- 6.15 The CHELATE randomised trial, although a good quality trial, which compared trientine 4HCl to DPA in patients stabilised on DPA, included patients receiving maintenance treatment who were not intolerant of DPA, i.e. a population that was not consistent with the listing proposed for the PBS. Thus, the results simply supported the claim that DPA and trientine treatment both result in urinary copper excretion probably sufficient to prevent copper re-accumulation in the maintenance phase of treatment.
- 6.16 The meta-analysis comparing chelation and BSC presented in the submission (adapted from the published systematic review by Appenzeller-Herzog 2019 to include results from Scheinberg 1987) confirmed that chelation was more effective than no treatment with respect to mortality (see Figure 1) but were of insufficient quality to be used to accurately estimate an effect size. In addition, during the evaluation it was not possible to replicate the data reported in the submission from two of the five studies (Goldstein 1968 and Sternlieb 1968) that were presented in the Appenzeller-Herzog 2019 meta-analysis. The PSCR noted that the results of the individual studies provided a relatively constant effect size with a low level of heterogeneity between the studies ($I^2 = 0\%$).

Figure 1: Forest plot of meta-analysis of mortality outcomes between DPA and no treatment



Source: Figure 2.6, p69 of the submission.

- 6.17 The ESC considered the clinical evidence to be of poor quality and the treatment effect in the proposed PBS population remained uncertain given the nature of the studies and the age of the data. However, the ESC acknowledged that the effect size shown across the studies comparing chelation to no chelation was consistent and also reflected the known benefit of chelating agents as life-saving treatment in clinical practice.

Comparative harms

- 6.18 Adverse events as reported in the CHELATE trial are shown below.

Table 5: Summary of TEAEs in the CHELATE trial

	Penicillamine baseline period (all patients received DPA - 12 weeks)		Post-randomisation period (24 weeks)	
	DPA ^a (N=27)	Trientine 4HCl ^a (N=26)	DPA (N=27)	Trientine 4HCl (N=26)
TEAEs	16 (59.3%)	13 (50.0%)	17 (63.0%)	14 (53.8%)
TEAE severity				
Mild	11 (40.7%)	7 (26.9%)	9 (33.3%)	8 (30.8%)
Moderate	5 (18.5%)	6 (23.1%)	8 (29.6%)	6 (23.1%)
Severe	0	0	0	0
Treatment-related TEAE	4 (14.8%)	5 (19.2%)	3 (11.1%)	9 (30.8%)
SAEs	1 (3.7%)	1 (3.8%)	3 (11.1%)	0
Treatment-related SAEs	0	0	1 (3.7%)	0
Fatal TEAE	0	0	0	0
TEAEs leading to dose modification ^b	1 (3.7%)	1 (3.8%)	2 (7.4%)	2 (7.7%)

Source: Table 2.30, p84 of the submission.

4HCl = tetrahydrochloride; DPA = D-penicillamine; SAE = serious adverse event; TEAE = treatment-emergent adverse event

^a Treatment assignment in the post-randomisation period.

^b Dose increase, decrease, interruption or withdrawal.

6.19 Adverse events were common; however, there were no treatment-related severe adverse events in trientine 4HCl-treated patients. The submission reported the following adverse events in trientine 4HCl-treated patients in the post-randomisation period: abdominal pain, abnormal/soft faeces soft, dry mouth, alanine aminotransferase (ALT) increased, alopecia and rash/rash generalised. Only one patient discontinued trial treatment because of an adverse event (a patient receiving trientine 4HCl who developed a rash; CSR p73).

6.20 Reporting of adverse events in the observational studies was heterogenous, so precise estimates of events are uncertain.

Benefits/harms

6.21 The naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of trientine 4HCl and BSC. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.22 The submission claimed that trientine and DPA were non-inferior, based on observational studies comparing trientine 2HCl and DPA, and then claimed that chelation therapy is superior to BSC, based on DPA studies. Noting the acceptance by TGA of the equivalence of between trientine 4HCl to trientine 2HCl, the submission therefore described trientine 4HCl as superior in terms of effectiveness compared to BSC. The ESC considered that this claim could be accepted on the basis of chelation treatment with either DPA or trientine having been accepted as effective and potentially lifesaving in the treatment of WD for approximately 50 years; however, the poor quality of the available studies meant that the estimation of an effect size was unreliable. In addition, the care described in the observational studies of chelation

versus BSC was unlikely to be consistent with contemporary clinical practice. The PBAC considered that the claim of superior comparative effectiveness, although reasonable, was poorly supported by the data.

- 6.23 The ESC noted that if trientine 4HCl was non-inferior to DPA, as claimed in the submission, then the price of trientine 4HCl should be more comparable to that of DPA.
- 6.24 The submission described trientine 4HCl as inferior in terms of safety compared to BSC. The PBAC considered that this claim was probably reasonable on the basis of extensive use of and experience with trientine but was poorly supported by the evidence presented.

Economic analysis

- 6.25 The submission presented a cost-utility analysis comparing trientine 4HCl with BSC. As noted above, while historical use indicated that trientine 4HCl was superior to BSC in terms of effectiveness, the poor quality of the studies meant that the estimation of an effect size was unreliable.
- 6.26 The table below outlines the model structure and key inputs.

Table 6: Summary of model structure, key inputs and rationale

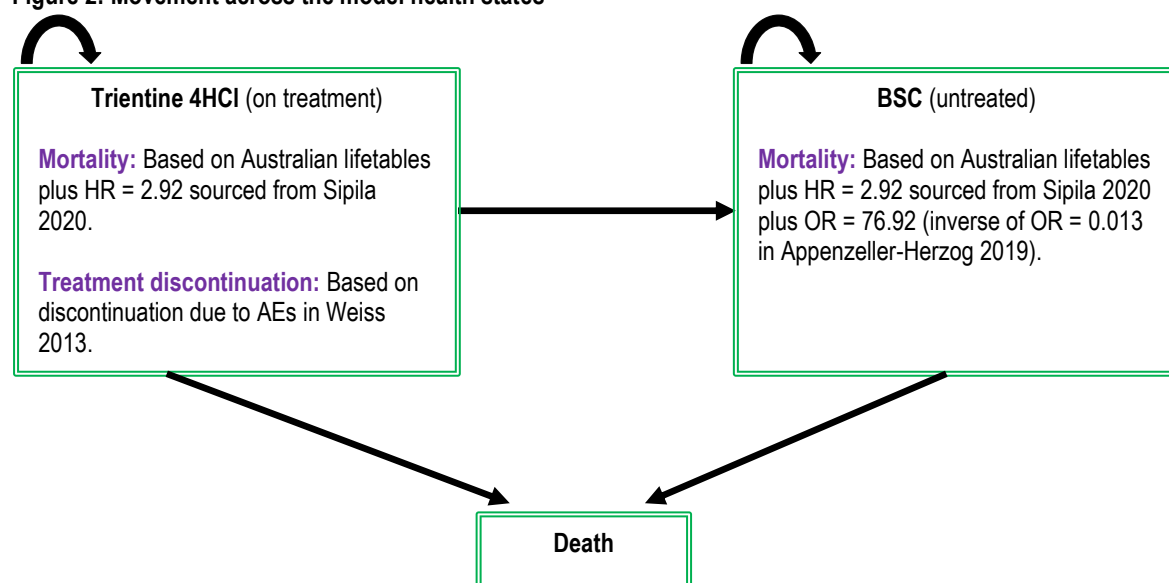
Component	Summary
Treatments	Trientine 4HCl versus BSC
Time horizon	Lifetime (80 years), with a starting age of 20 years.
Outcomes	QALYs, LYs, liver transplant and death. Liver transplant was included only as a sensitivity analysis.
Methods used to generate results	Markov model
Health states	Three health states: on treatment, untreated and dead. Two additional health states were included for sensitivity analyses: post liver transplant year 1; post liver transplant subsequent years
Cycle length	1 year
Transition probabilities	Mortality: Australian lifetables, adjusted to reflect a WD population using Sipila 2020 and BSC mortality based on Appenzeller-Herzog 2019. Treatment discontinuation: Weiss 2013.
Extrapolation method	Extrapolation was not used; constant treatment effect applied.
Health related quality of life	Literature-based (Schaefer 2016) On treatment: 0.86; untreated: 0.65
Discount rate	5%

Source: Table 3-1, p97; Table 3-16, p121 of the submission

4HCl = tetrahydrochloride; BSC = best supportive care; LY = life year; QALY = quality adjusted life year; WD = Wilson Disease

- 6.27 The following diagram sets out the structure of the economic model and key inputs.

Figure 2: Movement across the model health states

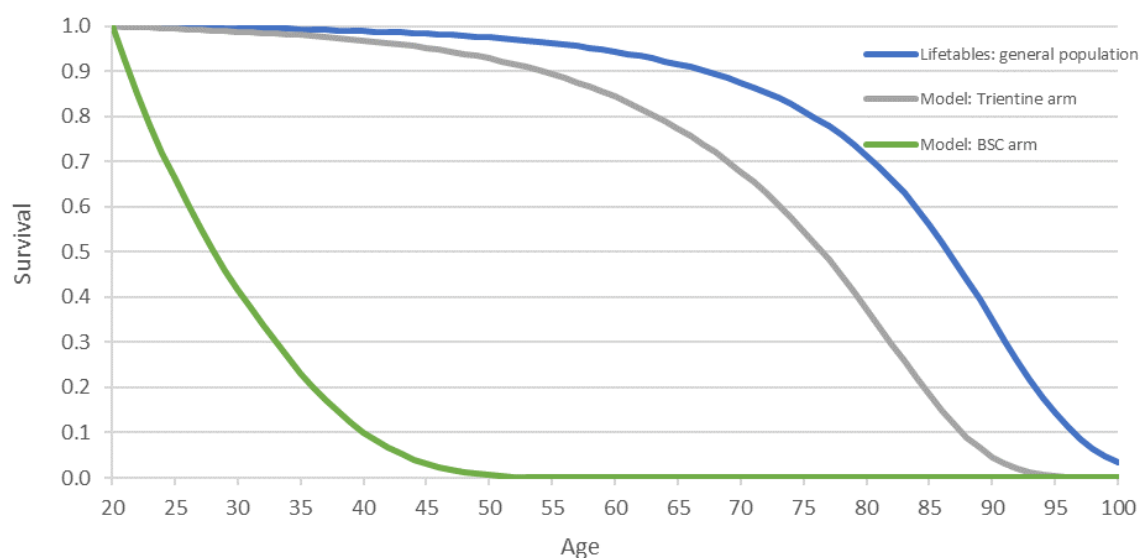


Source: Developed during the evaluation.

4HCl = tetrahydrochloride; BSC = best supportive care; HR = hazard ratio; OR = odds ratio

- 6.28 The PSCR stated that little clinical evidence was required as the economic model was very simple in its structure and was predicated on the proven claim that chelation therapy improves life expectancy relative to no chelation therapy. The PSCR stated that therefore, the only clinical evidence required for the economic model was the extent or magnitude to which life expectancy is improved. The ESC considered that the economic model was overly simplistic (e.g. it was missing liver transplant states) resulting in structural uncertainties.
- 6.29 While a Markov model was used, and survival was a key component of the model, the application of mortality in the model was not standard as extrapolation was not applied over the 80-year model duration. Instead, survival was based on a constant hazard ratio (HR) value for trientine 4HCl patients and odds ratio (OR) value for BSC patients across the lifetime model duration (see Figure 3). While the model incorporated lifetable-based mortality, the assumption that a constant mortality risk is applied to lifetable values across the 80 years of the model was not adequately supported. The ESC considered that patients would have a mortality risk associated with (i) WD and (ii) receiving trientine 4HCl or BSC, and that the risks would most likely change over time. The pre-PBAC response stated that this was how the model was operating, but the PBAC noted that the risks in the model changed as the background mortality changed, whereas the HR and OS values applied remained constant.

Figure 3: Estimated survival in the trientine 4HCl and BSC arms of the model, compared to the general population



Source: Figure 3-10, p114 of the submission.

4HCl = tetrahydrochloride; BSC = best supportive care

- 6.30 In addition, the use of the HR and OR values, which are different measures^{5,6}, was not justified by the submission. The submission also did not justify the use of an inverse-sourced OR from Appenzeller-Herzog 2019 for BSC survival. This was despite the submission stating that survival from the studies included in the Appenzeller-Herzog 2019 meta-analysis were unlikely to be applicable to current practice due to the dates of the studies (1968, 1973, 2001). The PSCR stated that the inverse OR from Appenzeller-Herzog 2019 was appropriate as the source data calculated the odds of death without treatment relative to with treatment and the model is using this ratio to derive the odds of death without treatment from the odds of death with treatment and, given the OR and its inverse are symmetrical, this is mathematically sound. The ESC agreed that the inversion of the OR from Appenzeller-Herzog 2019 was mathematically sound; however, considered that the use of two different measures to determine transition probabilities in the model was not appropriately justified, particularly as the HR measures an instantaneous difference in risk which may have been adjusted (see Sipila 2020), whereas an OR summarises an entire study.
- 6.31 The Sipila 2020 study, which was the source of the HR used for trientine 4HCl survival, was based on 33 WD patients in Finland, of which 64% (N=21) were treated with DPA and 30% (N=10) were treated with trientine, compared to 6,600 age- and gender-matched controls. The submission did not include this study in the clinical evidence

⁵ Scott I. Interpreting risks and ratios in therapy trials. *Aust Prescr* 2008; 31:12–16.

⁶ George A, Stead T S, Ganti L. What's the risk: Differentiating risk ratios, odds ratios, and hazard ratios? *Cureus* 12(8): e10047. doi:10.7759/cureus.10047.

presented. In addition, the submission's claim of non-inferiority between trientine and DPA did not include mortality as an outcome, and it was difficult to quantify an advantage for trientine based on the available evidence.

- 6.32 The utility values applied in the model were sourced from Schaefer 2016, which was a cross-sectional study assessing quality of life (QoL) and risk for depression in 68 WD patients. The study provided SF-36 scores, which the submission mapped to utility values. The utility value for the overall WD population (0.86) was selected for use as the utility for the treated health state in the model. For the untreated health state, the submission applied the utility value sourced from Schaefer 2016 which represented the lowest quartile of SF-36 scores for WD patients (0.65). The submission did not adequately justify the assumption that the patients in the lowest quartile from Schaefer 2016 represented WD patients who were untreated. The Schaefer 2016 paper stated (p353) that analysis of this lowest quartile subgroup suggested that the group of WD patients was very heterogeneous (concerning age, gender and onset). The ESC noted that in addition, the publication stated (p352) that SF-36 scores were also analysed by type of medical treatment, and it was found that DPA-treated patients had better quality of life and higher SF-36 scores compared to patients treated with trientine or zinc. In particular, patients treated with DPA had statistically significantly better total SF-36 scores compared to those receiving trientine treatment ($p=0.01$). The submission provided no discussion around the likelihood that QoL may decrease for patients who are intolerant to DPA.
- 6.33 Although the proposed PBS population included paediatric patients, the economic model included only adult patients, aged 20 and older. While it was likely that it would be difficult to find utility values for a paediatric population, it was noted that the financial estimates were based on a population comprised of 82% adults and 18% paediatric patients. The ESC noted that it would have been more appropriate for the submission to consider the applicability of the model results to a paediatric population. The pre-PBAC response stated that the patient baseline characteristics in the applied in the model were based on Weiss 2013 which included both adults and children, and therefore the model reflects the costs and outcomes of the total PBS population.

Table 7: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ [redacted] /QALY gained
Clinical evidence	The overall poor quality of the studies presented did not provide a basis for a quantitative estimate of the effect size for trientine versus BSC. Therefore, the accuracy of the modelled economic evaluation is limited.	High; favours trientine 4HCl
Trientine 4HCl price	As discussed in paragraph 3.3, the requested DPMQ for trientine 4HCl is high (\$ [redacted]).	High; arbitrarily reducing the DPMQ of trientine 4HCl to \$ [redacted] reduced the ICER to \$ [redacted] ² /QALY.
Trientine 4HCl dose	The assumed dose was based on 2017-2018 SAS dosing (1,000 mg/day trientine 2HCl). As 0.668 mg of trientine 4HCl is similar to 1 mg trientine 2HCl, a dose of 668 mg/day for trientine 4HCl was estimated (1000 mg × 0.668). The SAS dosing calculated by the submission may or may not represent what is used on an individual patient basis. The model also assumed 100% compliance for trientine dosing, which may not be observed in practice, as the CHELATE trial and literature has reported non-compliance. Overall, the dose used may not accurately reflect what will be used in clinical practice.	High: Decreasing the dose to the minimum recommended dose of 450 mg/day reduced the ICER to \$ [redacted] ² /QALY; increasing the dose to the maximum recommended dose of 975 mg/day increased the ICER to \$ [redacted] ³ /QALY.

Source: Compiled during the evaluation.

2HCl = dihydrochloride; 4HCl = tetrahydrochloride; BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SAS = Special Access Scheme

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$75,000 to < \$95,000

³ \$155,000 to < \$255,000

6.34 The submission did not provide a stepped economic evaluation. Results of the economic evaluation are in the table below.

Table 8: Results of the economic evaluation

Component	Trientine 4HCl	BSC	Increment
Costs (\$)	[redacted]	\$7,785	[redacted]
LY	17.558	6.946	10.612
Incremental cost/extra LY gained (base case)			[redacted] ¹
QALY	14.984	4.515	10.469
Incremental cost/extra QALY gained (base case)			[redacted] ²

Source: Table 3-25, p131 of the submission

4HCl = tetrahydrochloride; BSC = best supportive care; LY = life year; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$135,000 to < \$155,000

6.35 The ICER per QALY reflected the high treatment costs for trientine 4HCl (99.5% of incremental cost in the model is drug cost). Overall, the model results were not likely to be reliable given the varying effect sizes used for survival (HR=2.92 for trientine 4HCl; inverse OR=76.92 for BSC) and their application in the model and the structural uncertainties of the model.

6.36 The submission did not include liver transplant in the base case modelled evaluation on the basis that adding the costs and outcomes of liver transplant would increase model uncertainty. Instead, the submission provided a sensitivity analysis including

liver transplant. This analysis assumed that 10% of patients who were to die due to WD in the base case model would instead be transitioned to liver transplant. The inputs to the model for inclusion of liver transplant are provided in the table below.

Table 9: Model inputs for inclusion of liver transplant

Parameter	Input	Source
Proportion receiving liver transplant	10%	Assumption
Mortality		
First year post-transplant	10%	ANZLITR 2019
Subsequent years post-transplant	SMR: 2.5 relative to general population	Aberg 2015
Utility values		
First year post-transplant	0.65	Same as WD untreated (assumption)
Subsequent years post-transplant	0.86	Same as WD on treatment (assumption)
Cost		
Index procedure	\$167,654	NHCDC Round 22 DRG version 10
Annual immunosuppression cost	\$7,306	Calculated ^a

Source: Table 3-34, p136 of the submission.

ANZLITR = Australia & New Zealand Liver and Intestinal Transplant Registry; NHCDC = National Hospital Cost Data Collection; SMR = standardised mortality rate; WD = Wilson Disease

^a The cost of tacrolimus is \$571.50 per 100 units on the PBS (item 10871E). A mean patient weight of 70kg and a mean dose of 0.1 mg/kg/day were assumed. Ongoing immunosuppression with tacrolimus was estimated to cost \$7,306 per year [$\$571.50/100 \times (0.1 \times 70/2) \times 365.25$].

6.37 The submission provided little discussion of the model inputs used for liver transplant and there was no discussion of why a proportion of 10% receiving transplant was used, no discussion of the mortality values used, nor was there discussion of why utility values in the first year were assumed to be the same as untreated WD patients. The source for mortality in subsequent years post-transplant (Aberg 2015) was a Nordic liver transplant registry based on data from patients who underwent a liver transplant between 1985 and 2009. It is probable that survival in these patients may not accurately represent survival for liver transplant patients in current clinical practice. Further, while the registry data included an 'other' category for reason for transplantation, there was no indication of whether any included patients had WD. Results of the sensitivity analysis for liver transplant are provided in the table below.

Table 10: Sensitivity analysis – inclusion of liver transplant

Component	Trientine 4HCl	BSC	Increment
Receiving liver transplant	10% ^a		
Costs			
Drug cost (\$)		\$0	
Terminal care cost	\$1,356	\$7,912	-\$6,557
Transplant cost	\$11,346	\$16,681	-\$5,335
Immunosuppressant cost	\$1,049	\$7,786 ^b	-\$6,737
Total cost (\$)		\$32,380	
Life expectancy	70.5	33.7	36.8
Time on treatment	17.007	0.000	17.007
LY	17.702	8.012	9.690
Incremental cost/extra LY gained (base case)			
QALY	15.106	5.418	9.688
Incremental cost/extra QALY gained (base case)			

Source: Table 3-35, p137 of the submission

4HCl = tetrahydrochloride; BSC = best supportive care; LY = life year; QALY = quality adjusted life year

^aWhile the submission stated (Table 3-34, p136) and the model Excel workbook indicated (cell C82 of worksheet 'Inputs') that 10% of patients would receive a liver transplant, Table 3-35 of the submission indicated (p137) that 6.8% of trientine 4HCl and 9.9% of BSC patients received liver transplant.

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

- 6.38 The submission concluded that the application of liver transplant to 10% of patients who would otherwise have died from WD did not significantly impact the cost-effectiveness of trientine 4HCl versus BSC. The base case ICER including liver transplant of \$135,000 to < \$155,000 per QALY gained was unlikely to accurately estimate the cost-effectiveness of trientine 4HCl, given the highly uncertain mortality data used and the assumptions applied. Although the assumptions were uncertain, the ESC considered that the inclusion of cost and outcomes associated with liver transplant was appropriate to include in the base case.
- 6.39 The submission also provided a series of sensitivity analyses addressing inputs such as time horizon, mortality risk, trientine 4HCl dose and utility values. Results of key analyses are summarised below.

Table 11: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change ICER
Base case	█	10.469	█ ¹	-
Discount rate (base case: 5%)				
3.5%	█	14.238	█ ²	-6%
0%	█	36.178	█ ⁴	-17%
Time horizon (base case: lifetime – 80 years)				
10 years	█	2.982	█ ³	+52%
30 years	█	8.137	█ ¹	+8%
Mortality risk (base case: HR = 2.92 for WD vs. general population; OR = 76.92 for treated vs. untreated)				
HR = 1.0 for WD vs. general population	█	8.715	█ ³	+26%
HR = 5.0 for WD vs. general population	█	11.072	█ ²	-9%
OR = 38.46 for treated vs. untreated	█	8.907	█ ³	+18%
HR = 1.0 for WD vs. general population and OR = 38.46 for treated vs. untreated	█	7.297	█ ³	+50%
Trientine 4HCl dose (base case: 4.45 tablets per day, i.e. 668 mg/day)				
3 tablets/day (450 mg)	█	10.469	█ ⁵	-33%
6.5 tablets/day (975 mg)	█	10.469	█ ³	+46%
Maintenance phase (base case: not included)				
1 tablet/day (150 mg) from 5 years	█	10.469	█ ⁶	-57%
3 tablets/day (450 mg) from 5 years	█	10.469	█ ⁴	-24%
1 tablet/day (150 mg) from 10 years	█	10.469	█ ⁵	-43%
3 tablets/day (450 mg) from 10 years	█	10.469	█ ⁴	-18%
DPMQ of trientine (base case: \$ █)				
DPMQ = \$ █	█	10.469	█ ²	-13%
DPMQ = \$ █	█	10.469	█ ⁵	-33%
DPMQ = \$ █	█	10.469	█ ⁶	-53%

Source: Table 3-26 to 3-35, p132-137 of the submission.

4HCl = tetrahydrochloride; AE = adverse event; DPMQ = dispensed price for maximum quantity; HR = hazard ratio; ICER = incremental cost effectiveness ratio; OR = odds ratio; QALY = quality adjusted life year; WD = Wilson Disease

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$115,000 to < \$135,000

³ \$155,000 to < \$255,000

⁴ \$95,000 to < \$115,000

⁵ \$75,000 to < \$95,000

⁶ \$55,000 to < \$75,000

6.40 The model demonstrated considerable sensitivity to model inputs which indicated that the model base case was not likely to estimate the cost-effectiveness of trientine 4HCl accurately.

6.41 The ESC also noted that the ICER was highly sensitive to the dose and DPMQ of trientine 4HCl applied. Arbitrarily applying a DPMQ of \$ █ for trientine 4HCl resulted in a revised base case ICER of \$75,000 to < \$95,000 per QALY.

6.42 The ESC considered that the model was not reliable for decision making as:

- The poor quality clinical data meant that the estimation of an effect size was unreliable;

- The model structure was very simplistic, with survival based on a constant HR for trientine 4HCl patients and a constant OR for BSC patients. The ESC considered that mortality risks would change over time (see paragraph 6.29); and
- The inputs applied to the liver transplant sensitivity analysis were highly uncertain, particularly in terms of the mortality values applied (see paragraphs 6.36 and 6.37).

Drug cost/patient/year

Table 12: Drug cost per patient for trientine 4HCl and BSC

	Trientine 4HCl		BSC
	Description	Cost (\$)	Description
Treatment cost – economic model			
DPMQ	Requested price	█	It was assumed no medicines were included in BSC for treatment of WD, thus no cost was applied.
Dose/day	668 mg	-	
Tablets/day	4.45	-	
Cost (\$)/tablet	█ ÷ 144 (pack size) =	█	
Cost (\$)/day	█ × 4.45 =	█	
Cost(\$)/year	█ × 365.25 =	█	
Treatment cost – financial estimates			
DPMQ	Adjusted for adult (82%) and paediatric use (18%)	█	Not included
Tablets/day	4.45	-	
Cost (\$)/tablet	█ ÷ 144 (pack size) =	█	
Cost (\$)/day	█ × 4.45 =	█	
Cost (\$)/year	█ × 365.25 =	█	

Source: Section 3.6.1, p126 of the submission; worksheet 'Inputs' of the Excel workbook 'Section 3_CEA_Cuprior'.

4HCl=tetrahydrochloride; BSC=best supportive care; DPMQ = dispensed price for maximum quantity; WD = Wilson Disease

6.43 For comparison, the cost per patient per year for DPA treatment would be \$1,943, assuming a dose of 1,750 mg/day (recommended daily dose in the Product Information is 1,500 mg to 2,000 mg) and use of 250 mg tablets (PBS 2838J).

Estimated PBS usage & financial implications

6.44 This submission was considered by DUSC. The submission applied a prevalence-based epidemiological approach to estimate the number of patients eligible for treatment with trientine 4HCl. The table below summarises the inputs used for the financial estimates.

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Table 13: Key inputs for financial estimates

Component	Data source
Epidemiology	
Prevalence data	Australian population aged ≥5 years: ABS 3222.0 Series B Prevalence of WD: 3.3 per 100,000, based on Scheinberg and Sternlieb 1984.
Eligible patients	The number of eligible patients was multiplied by a diagnosis rate of 50% (Sandahl 2020) then multiplied by a DPA usage rate of 75% (submission assumption) and then multiplied by 30% for those intolerant to DPA (Ferenci 2012; Socha 2018; Weiss 2013).
Utilisation	
Uptake rate	Sponsor assumption: █% in Year 1 increasing to █% by Year 6.
Treatment duration	Lifetime
Compliance	Discontinuation rate 1.4% annually (Weiss 2013)
Number of scripts	Adults: 4.45 tablets/day; 11.28 packs initiation per year; 22.56 packs continuation per year; 1.88 packs/month Paediatric patients: 2.75 tablets/day; 6.97 packs initiation per year; 13.94 packs continuation per year; 1.16 packs per month Weighted average monthly packs: 1.75
Cost of medicines	
Trientine 4HCl	Requested price: \$█ Adjusted to account for adult (82%) and paediatric (18%) use: \$█
Patient co-payment	Co-payment calculated as \$20.57 for PBS and \$6.48 for RPBS.
Impact on other medicines	
Other agents	None.
MBS usage and costs	
MBS items	None.

Source: Table 4-2, p141; Table 4-3, p143; Table 4-9, p148; Table 4-10, p149 Table 4-11, p149; Table 4-12, p150 of the submission.

4HCl = tetrahydrochloride; ABS = Australian Bureau of Statistics; DPA=D-penicillamine; WD = Wilson Disease

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² <500

6.45 The estimated patient numbers, prescription numbers and costs for the PBS listing of trientine 4HCl for the treatment of WD are provided below.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated ^a						
Cumulative (tried at least once)	1	1	1	1	1	1
Annual	1	1	1	1	1	1
Number of scripts dispensed ^b						
	2	2	2	2	2	2
Estimated financial implications of trientine 4HCl						
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Net financial implications						
Net cost to PBS/RPBS	3	3	3	3	3	3

Source: Table 4-13, p150 of the submission.

4HCl = tetrahydrochloride

^a The submission presented numbers which represented partial patients, as rounding was not used.

^b Assuming 1.75 monthly packs, weighted across adult and paediatric use, as estimated by the submission.

The redacted values correspond to the following ranges:

¹ <500

² 500 to < 5,000

³ \$0 to < \$10 million

- 6.46 The total cost to the PBS/RPBS of listing trientine 4HCl was estimated to be \$0 to < \$10 million in Year 6, and a total of \$30 million to < \$40 million over the first 6 years of listing.
- 6.47 The DUSC noted that the number of treated patients and scripts was heavily influenced by the submission’s assumptions that a 50% diagnosis rate (Sandahl 2020) should be applied to prevalent patients, that only 75% of patients are treated with DPA and, of those, 30% are intolerant to DPA. DUSC considered the 50% diagnosis rate and the assumption that 75% of patients would use DPA as a first-line treatment were underestimated. The 50% diagnosis rate was based on a 1984 study and DUSC considered that it was likely that screening and diagnosis of WD would have improved since. The DUSC also considered that it was not reasonable to assume that 75% of patients are treated with DPA when no other pharmacological treatment is available. DUSC noted that this may have been an attempt to account for asymptomatic patients.
- 6.48 If the 50% diagnosis rate and 75% DPA usage rate were removed from the estimates, then the number of treated patients increased by more than 2.5 times, as did the estimated net cost to the PBS/RPBS, to \$90 million to < \$100 million over the first 6 years of listing.
- 6.49 The financial estimates presented by the submission assumed a dose of 668 mg/day (4.45 tablets) for adults and 2.75 tablets per day for children. The adult dose was sourced from 2017/18 Special Access Scheme (SAS) applications, which may or may not represent what is used on an individual patient basis.
- 6.50 The financial estimates were also adjusted for adult (82%) and paediatric use (18%), which decreased the requested DPMQ from \$ [redacted] to \$ [redacted]. It could not be

determined if those adult and paediatric proportions would be observed in clinical practice.

- 6.51 The DUSC also noted that there was a potential for use beyond the proposed restriction into (i) the first line population; (ii) patients aged less than 5 years; and (iii) patients with neurological deterioration misinterpreted for DPA intolerance rather than disease progression.

Financial Management – Risk Sharing Arrangements

- 6.52 The submission proposed a cap-based risk share arrangement (RSA) could be used to protect against use of trientine 4HCl in patients who would not otherwise be considered intolerant to DPA. The submission indicated the use and cost of trientine 4HCl could form the basis of a financial cap, with the extent of the rebate for expenditure beyond the cap to be negotiated between the sponsor and the Department of Health.
- 6.53 The sponsor claimed that PBS listing of trientine 4HCl at a cost-effective price and with an appropriate RSA in place is financially more sustainable for the Australian healthcare system and more equitable than the ad hoc and uncapped funding at undisclosed prices being conducted through public hospitals. The ESC considered the submission has not demonstrated that trientine 4HCl is cost-effective at the requested price, or at the price adjusted for adult and paediatric usage applied in the financial estimates. It is likely that adult and paediatric use would have to form part of the RSA.
- 6.54 The ESC considered that a RSA based on an appropriate DPMQ and usage estimates for trientine 4HCl would be required to minimise the risk of use beyond the proposed restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend trientine tetrahydrochloride (4HCl) for the treatment of patients with Wilson Disease (WD) intolerant to penicillamine/D-penicillamine (DPA) therapy. Although the PBAC accepted that chelation therapy prevents the progression of WD, the PBAC considered that the proposed place in therapy for trientine 4HCl and the nomination of best supportive care (BSC) as the comparator were unacceptable as they were inconsistent with current clinical practice and the available treatment guidelines. The PBAC therefore considered that the economic evaluation that compared trientine 4HCl with BSC was uninformative. In addition, the PBAC considered that the financial estimates were high, particularly at the proposed price. The PBAC considered that a cost minimisation approach versus DPA would be more appropriate.
- 7.2 The PBAC noted that the submission proposed that trientine 4HCl be used as a second-line treatment in patients intolerant to DPA. The PBAC noted that although this aligned

with the TGA indication, it was not consistent with the three available treatment guidelines developed for WD from the American Association for the Study of Liver Diseases (AASLD), the European Association of the Study of the Liver (EASL) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)⁷, nor was it consistent with some state-based hospital formularies, all of which considered that the initial therapy should be a chelating agent consisting of either DPA or trientine.

- 7.3 The PBAC noted that the submission nominated BSC as the comparator in DPA intolerant patients. Noting the available guidelines and the clinical evidence presented, the PBAC considered that the proposed place in therapy for trientine 4HCl should be line agnostic. Therefore, the PBAC considered that the appropriate comparator was DPA.
- 7.4 The PBAC noted that the clinical evidence presented by the submission consisted of:
- pharmacokinetic studies, which were used to establish the equivalence of trientine 4HCl with the existing trientine dihydrochloride (2HCl) products;
 - three observational studies evaluating DPA and trientine (mostly 2HCl) and an unpublished randomised controlled trial (CHELATE) comparing trientine 4HCl to DPA; and
 - a meta-analysis of four observational studies, plus data from one additional study, comparing chelation therapy versus best supportive care.
- 7.5 The PBAC considered that the quality of the evidence presented was poor and that risk of bias was high in all the presented studies.
- 7.6 The PBAC noted that these studies were used to inform a 2-step indirect treatment comparison, which firstly compared trientine 4HCl to DPA and then compared chelation therapy, which consisted of DPA only, to BSC.
- 7.7 The PBAC noted that the submission claimed that trientine 4HCl was non-inferior to DPA in terms of effectiveness. The PBAC had low confidence in the evidence presented as the data were of too low a quality to determine quantitative estimates of the effect size between trientine 4HCl and DPA in terms of similarity or difference. However, the PBAC considered that the claim that trientine 4HCl and DPA were non-inferior in terms of efficacy was consistent with the accepted clinical approach to treatment and the available guidelines. The PBAC considered that it was likely that trientine 4HCl was superior compared to DPA in terms of safety, but this was poorly supported by the evidence presented.
- 7.8 The PBAC considered that the claim that chelation therapy, and thus trientine 4HCl,

⁷ Saroli Pulumbo C, Schilsky ML. Clinical practice guidelines in Wilson disease. *Ann Transl Med.* 2019;7(Suppl 2):S65.doi:10.21037/atm.2018.12.53

was superior to BSC in terms of efficacy was reasonable, on the basis of chelation treatment being accepted as an effective and lifesaving treatment for WD, but the magnitude of benefit was poorly supported by the evidence presented. The PBAC considered that the claim the trientine was inferior in terms of safety compared to BSC could not be assessed based on the evidence presented. The PBAC reiterated that the most informative comparison was between trientine 4HCl and DPA.

- 7.9 The PBAC noted that the submission presented a cost-utility analysis comparing trientine 4HCl with BSC. The PBAC considered that the results of the economic analysis were highly uncertain as the studies presented did not provide a basis for a quantitative estimate of effective size for trientine 4HCl versus BSC, the underlying clinical data that supported most of the input parameters was of a poor quality and the base case did not include the costs and outcomes of liver transplant.
- 7.10 The PBAC also noted that the economic model was highly sensitive to both the dose and the price of trientine 4HCl applied in the model.
- 7.11 Noting the available guidelines and the claim in the submission that trientine 4HCl was non-inferior to DPA, the PBAC considered that the economic model was uninformative and that the substantially higher price requested for trientine 4HCl compared to DPA was not justified. The PBAC considered that the economic evaluation should be based on a cost minimisation approach versus DPA for both initial and maintenance treatment.
- 7.12 The PBAC noted that the estimated financial implications provided in the submission. The PBAC considered that the epidemiology of WD was not well established and that the modelling assumptions applied were not well justified or supported by the evidence. The PBAC also noted that the estimates were sensitive to the assumed dose and the proportions of adult and paediatric patients. Overall, the PBAC considered that the estimates were high, primarily due to the price of trientine 4HCl requested.
- 7.13 The PBAC considered that if trientine 4HCl was cost minimised to DPA a risk sharing arrangement would not be required.
- 7.14 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for trientine 4HCl using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- A line-agnostic place in therapy, with nomination of DPA as the primary comparator
 - An economic evaluation based on a cost minimisation approach versus DPA
 - Utilisation and financial estimates updated to align with the revised place in therapy.
- 7.15 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle

or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Orphalan is disappointed with the PBAC's decision not to recommend a PBS listing for trientine 4HCl to treat WD. We are concerned that in this setting, there is now a lack of access to any effective chelating therapies to treat this life-threatening condition. We will continue to work with the PBAC process to help ensure equitable and sustainable access to trientine 4HCl for the patient population intolerant to DPA.