

## 5.16 TRIENTINE, Capsule containing trientine dihydrochloride 250 mg (equivalent to 166.7 mg trientine), Trientine Waymade<sup>®</sup>, Clinect Pty Ltd

### 1 Purpose of submission

- 1.1 The Category 1 submission requested Authority Required listing for trientine dihydrochloride (2HCl) for the treatment of patients with Wilson Disease (WD) intolerant to penicillamine/D-penicillamine (DPA) therapy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus no active treatment.

**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 penicillamine therapy.   |
| Intervention   | Trientine dihydrochloride (2HCl). The recommended initial dose for adults is 750 mg to 1,250 mg per day in 2 to 4 divided doses. This may be increased to a maximum of 2,000 mg per day. The recommended initial dose for children is 20 mg/kg per day given in 2 to 3 divided doses. This may be increased to a maximum of 1,500 mg per day for patients aged 12 or under. |
| Comparator     | Placebo   |
| Outcomes       | Improvement of hepatic and/or neurological symptoms   |
| Clinical claim | In Wilson Disease patients intolerant to penicillamine, trientine is superior in efficacy and safety compared to no treatment.  |

Source: Table 1-1, p 13 of the submission and the Product Information

### 2 Background

#### **Registration status**

- 2.1 Trientine 2HCl was TGA registered on 11<sup>th</sup> of January 2021 for treatment of WD in patients who cannot tolerate DPA. The AUSPAR and approved Product Information were provided with the submission.

*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 DIHYDROCHLORIDE capsules 250mg, 100        | 200      | 5           | \$ [REDACTED]                | Trientine Waymade® Clinect Pty Ltd |

|                           |  |
|---------------------------|--|
| <b>Category/Program:</b>  | GENERAL – General Schedule (Code GE)   |
| <b>Prescriber type:</b>   | <input checked="" type="checkbox"/> Medical Practitioners  |
| <b>Episodicity:</b>       | Chronic  |
| <b>PBS indication:</b>    | Wilson Disease   |
| <b>Treatment phase:</b>   | Initial  |
| <b>Restriction:</b>       | <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)   |
| <b>Clinical criteria:</b> | Patient must have trialled and be intolerant to penicillamine therapy  |
| <b>Treatment phase:</b>   | Continuing   |
| <b>Prescriber type:</b>   | <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners  |
| <b>Restriction:</b>       | <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)   |
| <b>Clinical criteria:</b> | Patient must have previously received PBS-subsidised treatment with this drug for this condition<br>AND<br>Patient must be assessed by their treating physician to determine eligibility of continuing therapy |

- 3.1 The ESC considered that initial prescribing should be limited to a gastroenterologist, hepatologist or neurologist.
- 3.2 The requested dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] for 2 packs x 100 (200), 250 mg capsules was considerable. The submission did not justify the high requested price for trientine 2HCl. The Pre-Sub-Committee Response (PSCR) stated that the price offered for trientine 2HCl was well within the accepted global pricing range and is suitable for a rare, orphan disease treatment. The ESC noted that the NSW hospital formulary price of trientine 2HCl was \$ [REDACTED] for 100 x 250 mg capsules. The ESC noted that the hospital price for 200 x 250 mg capsules would be \$ [REDACTED] which was higher than the requested DPMQ of \$ [REDACTED] in the submission. The pre-PBAC response offered a reduced DPMQ of \$ [REDACTED] for 200 x 250 mg capsules (AEMP = \$ [REDACTED]) to compensate for the uncertainties in the economic model. The PBAC also noted the variation in hospital formulary pricing, as provided in the consumer comments below.
- 3.3 The proposed restriction positioned trientine 2HCl 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)<sup>1</sup>, 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 2HCl should be line agnostic.

- 3.4 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 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. The disease can present at any age, with the majority of patients diagnosed between 5 and 35 years. Asymptomatic patients are most often detected by targeted family screening. Symptoms at the time of the initial presentation, and those that have evolved undetected, are usually either hepatic or neurologic/neuropsychiatric. The submission stated that the prevalence is estimated to be 1 in 30,000 to 1 in 40,000 patients in Australia with patient numbers expected to range between 644 and 858 patients.
- 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.

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<sup>1</sup> 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

- 4.4 Trientine (as the tetrahydrochloride or dihydrochloride), 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; papers in US journals refer to trientine hydrochloride, which is the US approved name) 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, or for management of asymptomatic individuals identified through screening. 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 no active treatment as the comparator for DPA intolerant patients. The ESC advised that liver transplant may also be an option.
- 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 that no treatment represents a hypothetical comparator for establishing clinical and cost effectiveness of trientine 2HCl. The evaluation commented that in the maintenance phase of treatment, and for asymptomatic patients, zinc would be an appropriate comparator. The PSCR stated that zinc was not an appropriate comparator in the maintenance phase as zinc monotherapy is not registered or reimbursed for this condition. The ESC noted that zinc is recommended in the three available treatment guidelines<sup>2</sup> in the maintenance phase and considered it may be used for a proportion of patients.

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<sup>2</sup> 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

- 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***

- 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 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 2HCl versus no active treatment, 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 three observational studies evaluating DPA and trientine and a published meta-analysis of four observational studies of chelation therapy versus best supportive care. These studies are listed in Table 2 below. The basis for the selection of these studies and the exclusion of others was poorly justified in the submission.
- 6.7 The indirect comparison was based on two steps: trientine vs DPA and chelation vs best supportive care.
- 6.8 Three observational studies were used to support the claim that trientine 2HCl is non-inferior to DPA with respect to a variety of clinical outcomes. The published meta-analysis was used to establish the benefit of chelation therapy versus best supportive care/no active treatment.

**Table 2: Studies and associated reports presented in the submission**

| Study ID                | Protocol title/ Publication title   | Publication citation                                  |
|-------------------------|---|---|
| Weiss 2013              | Weiss K H, Thirik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson Disease.   | <i>Clin Gastroenterol Hepatol</i> 2013; 11:1028-1035. |
| Weiss 2018              | Weiss KH, Manolaki N, Zuin MG, et al. Long term outcomes of treatment with trientine in Wilson disease: final results from a multicentre study in patients withdrawn from d-penicillamine therapy.              | <i>J Hepatol</i> 2018;68:S106-S107.                   |
| Weiss 2019              | Weiss KH, Pfeiffenberger J, Mohr I, et al. Safety and efficacy of trientine treatment in Wilson disease in patients withdrawn from d-penicillamine: final results from a prospective study.                     | <i>J Hepatol</i> 2019;70:e383-e624.                   |
| Appenzeller-Herzog 2019 | Appenzeller-Herzog, C, Mathes, T, Heeres, MLS, Weiss, KH, Houwen, RHJ, Ewald, H. Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies. | <i>Liver Int</i> 2019; 39: 2136–2152.                 |

Source: Table 2.1, p33 of the submission

6.9 The key features of the included evidence are summarised in Table 3. The risk of bias was high in all the observational studies. Data from all the publications were used in the model, as specified below.

**Table 3: Key features of the included evidence**

| Study ID                | N                          | Design   | Risk of bias      | Patient population  | Outcomes reported in submission  | Use in modelled evaluation  |
|-------------------------|----------------------------|--|-------------------|---|--|---|
| Weiss 2013              | 405                        | Retrospective case series  | High              | Patients with WD diagnosed from record review, identified from Heidelberg, Dresden, Dusseldorf, Vienna, Graz, Linz, EUROWilson Registry | Neurologic and hepatic symptoms<br>AEs leading to therapy discontinuation            | Proportion of patients with hepatic, neurological and hepatic + neurological WD symptoms; time to treatment discontinuation |
| Weiss 2018              | 77                         | Case series; not an inception cohort and overlap with previous Heidelberg series unclear | High              | Patients with WD  | Trientine treatment following DPA withdrawal; AEs, hepatic and neurological outcomes | Trientine dose  |
| Weiss 2019              | 52                         | Continuation of Weiss, 2018  | High              | Selected from patients in Weiss 2019; how 52 patients were selected was not reported  | AEs, hepatic and neurological outcomes   | Utility increment for trientine   |
| Appenzeller-Herzog 2019 | 23 studies; 2,055 patients | Systematic review  | High <sup>a</sup> | WD patients treated with DPA, trientine, TTM or zinc  | Mortality; asymptomatic/improved   | Relative risk of OLT/death for untreated patients   |

Source: Compiled from publications.

AE = adverse event; DPA = penicillamine; OLT = orthotopic liver transplant; TTM = tetrathiomolybdate; WD = Wilson disease

<sup>a</sup> Risk of bias remains high as the included studies were all high risk of bias.

6.10 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

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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 also 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 <sup>a</sup>  | Not reported   | Not reported    | 27; 4/27 not treated with DPA but reason not reported  |
| Sternlieb 1968 <sup>a</sup>  | 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 <sup>a</sup> | 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 <sup>a</sup>     | Paris, Geneva, Jerusalem   | 1969-1999       | 17 (Geneva 1, Jerusalem 2); first presentation with advanced liver disease: eligibility required symptoms < 2 months before admission, <b>and</b> haemolytic anaemia <b>and</b> "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 = penicillamine; NCC = non-ceruloplasmin bound copper concentration; UCE = urinary copper excretion

<sup>a</sup> Included in Appenzeller-Herzog 2019 meta-analysis.

6.11 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.

- 6.12 The PSCR noted that the evidence presented in the submission represented the only available evidence to inform a comparative evaluation against the nominated comparator, no active therapy. The PSCR stated that pragmatic decision making was required.
- 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 initial and 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 result of the ongoing studies. The PSCR stated that in the absence of trientine 2HCl there are no other suitable chelator treatments available for patients intolerant to DPA and therefore, there is no economic basis for the proposed cost minimisation approach proposed.

### Comparative effectiveness

- 6.14 The results of the observational studies (Weiss 2013 and Weiss 2018) and the meta-analysis (Appenzeller-Herzog 2019) as provided in the submission are presented below. The submission also provided an indirect comparison of trientine and DPA using the results from the published meta-analysis. There were insufficient data of adequate quality to estimate comparative effectiveness other than to state that chelation therapy with DPA or trientine prolongs life or avoids liver transplantation in patients with WD.

**Table 5: Rate of hepatic or neurologic improvement or worsening in all or only symptomatic patients by line of treatment at the end of the follow-up period (48 months) – Weiss 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%) | 0.859   | 12/31 (38.7%)          | 31/103 (30.1%) | 0.386   |
| Symptomatic            | 185/204 (90.7%)       | 25/27 (92.6%) | 1       | 12/16 (75%)            | 31/45 (68.9%)  | 0.757   |
| Hepatic worsening      |                       |               |         |                        |                |         |
| All                    | 4/295 (1.4%)          | 0/38 (0%)     | 1       | 0/31 (0%)              | 4/103 (3.9%)   | 0.573   |
| Symptomatic            | 4/204 (2%)            | 0/27 (0%)     | 1       | 0/16 (0%)              | 4/45 (8.9%)    | 0.565   |
| Neurologic improvement |                       |               |         |                        |                |         |
| All                    | 77/295 (26.1%)        | 11/38 (28.9%) | 0.699   | 3/31 (9.7%)            | 26/103 (25.2%) | 0.082   |
| Symptomatic            | 77/114 (67.5%)        | 11/20 (55%)   | 0.312   | 3/13 (23.1%)           | 26/51 (51%)    | 0.118   |
| Neurologic worsening   |                       |               |         |                        |                |         |
| All                    | 6/295 (2%)            | 4/38 (10.5%)  | 0.018   | 1/31 (3.4%)            | 8/103 (7.8%)   | 0.684   |
| Symptomatic            | 6/114 (5.3%)          | 4/20 (20%)    | 0.042   | 1/13 (7.3%)            | 8/51 (15.7%)   | 0.672   |

Source: Table 2-6, p49 of the submission.

DPA = penicillamine.

Reported p-values are based on a 2-tailed Fisher test.

**Table 6: Hepatic outcome over time (Weiss 2018)**

|   | 6 months  | 12 months | 24 months | 36 months | 48 months | Last follow-up |
|---|-----------|-----------|-----------|-----------|-----------|----------------|
| <b>Hepatic outcome, n (%)<sup>1</sup></b> |           |           |           |           |           |                |
| N   | 60        | 56        | 50        | 41        | 35        | 77             |
| Unchanged                                 | 12 (20.0) | 10 (17.9) | 9 (18)    | 16 (14.6) | 5 (14.3)  | 8 (10.4)       |
| Improved but not normal                   | 20 (33.3) | 18 (32.1) | 13 (26.0) | 13 (31.7) | 11 (31.4) | 21 (27.3)      |
| Improved to normal                        | 5 (8.3)   | 6 (10.7)  | 7 (14.0)  | 6 (14.6)  | 8 (22.9)  | 17 (22.1)      |
| Asymptomatic over duration of therapy     | 21 (35.0) | 20 (35.7) | 21 (42.0) | 15 (36.6) | 11 (31.4) | 27 (35.1)      |
| Worsened                                  | 2 (3.3)   | 2 (3.6)   | 0         | 1 (2.4)   | 0         | 4 (5.2)        |

Source: Table 2-7, p50 of the submission.

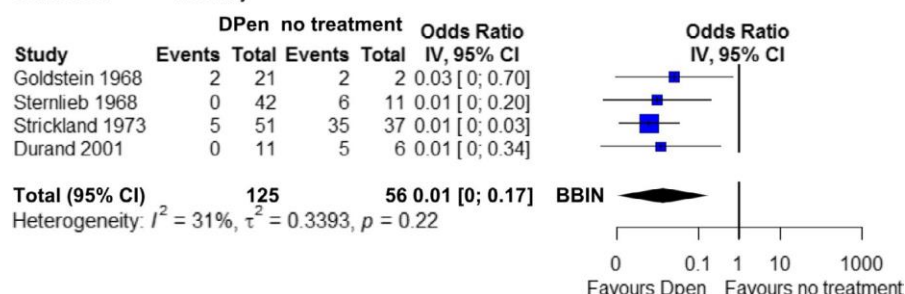
ITT = intention to treat; n = number of patients in the specified category with non-missing values.

<sup>1</sup> Percentages were based on the number (n) of patients with assessment of hepatic outcome/hepatic response.

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

**Comparison:** DPen versus no treatment

**Outcome:** mortality



Source: Table 2.13, p 58 of the submission.

6.15 The PSCR stated that all the studies included in the meta-analysis demonstrated a large reduction in mortality, despite the differences in study design and quality. The PSCR also noted that WD is a progressive disease and, if left untreated, is universally fatal.

6.16 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**

6.17 Adverse events reported from trientine treatment were infrequent. The results for the adverse events resulting in discontinuation of treatment as reported in Weiss 2013 are summarised below.

**Table 7: Adverse events leading to discontinuation of medical treatment (Weiss 2013)**

|   | DPA (n= 326) | Trientine (n = 141) |
|---|--------------|---------------------|
| Deaths                                    | 0            | 0                   |
| Number of treatments discontinued         | 94 (28.8%)   | 10 (7.1%)           |
| 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%)    | -                   |
| Haematuria                                | 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%)            |

Source: Table 2-11, p54 of the submission.

ANA = antinuclear antibodies; DPA = penicillamine

- 6.18 The submission claimed that trientine is well tolerated with fewer reported treatment-related side effects, with a safety profile more tolerable than DPA, based on the difference in treatment discontinuations due to adverse events. The risk of bias in this study is such that any differences in treatment discontinuation due to adverse events were likely to be due to confounding.
- 6.19 The submission also presented a summary of 27 studies that were included in the TGA dossier in support of the safety of trientine. While the submission listed adverse events that occurred in the studies, there was no information provided on study size, design and patient characteristics, and the submission provided no discussion of the types of events that were observed. The submission also provided no discussion of the possible implications of the adverse events that were observed, hence it was difficult to draw any conclusions regarding potential harms of trientine.

### **Benefits/harms**

- 6.20 The naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of trientine dihydrochloride and no active treatment. Accordingly, a benefits/harms table has not been presented.

### **Clinical claim**

- 6.21 The submission described trientine 2HCl as superior in terms of effectiveness compared to no active treatment, for patients intolerant to DPA. 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 lifesaving in the treatment of WD for approximately 50 years; however, the poor quality of the available studies meant that any estimation of an effect size was unreliable. The PSCR stated that although the exact magnitude of effect size was uncertain, all comparative literature demonstrates that chelation results in a large treatment effect and the absolute outcome of mortality is so drastically reduced, that any uncertainty would have a minimal impact on the claim that trientine is lifesaving for the majority of patients. The PBAC considered that the claim of superior comparative effectiveness, although reasonable, was poorly supported by the data.
- 6.22 The submission described trientine as superior in terms of safety compared to no active therapy. The ESC and 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**

- 6.23 The submission presented a cost-utility analysis comparing trientine 2HCl with no treatment. As noted above, while the therapeutic conclusion of superior effectiveness and safety for trientine 2HCl was probably reasonable given extensive use and experience with trientine, the overall poor quality of the studies presented did not provide a basis for a quantitative estimate of effect size for trientine versus no active treatment, which limited the accuracy of the modelled economic evaluation.
- 6.24 The table below outlines the model structure and key inputs.

**Table 8: Summary of model structure, key inputs and rationale**

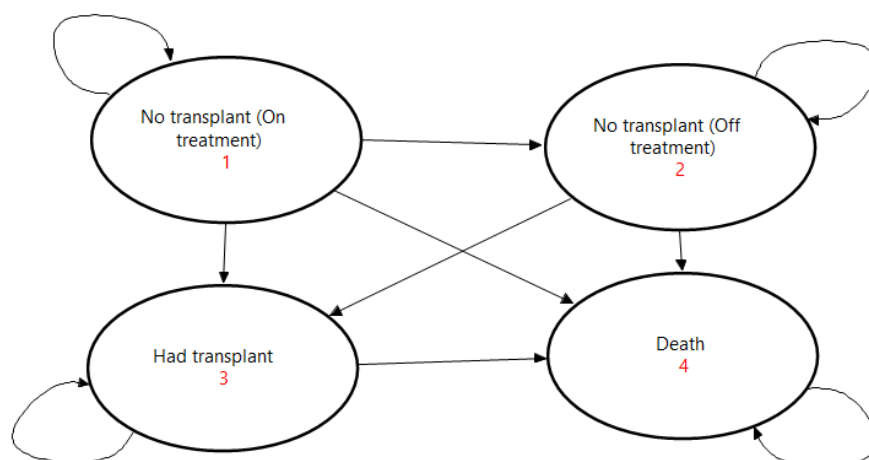
| Component                                   | Summary   |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
|---|---|----------------|---------|--------|--------------------|-------|---------------|-----------------------------------|-------|-------------|-------------------------|-------|---------------|----------------------------|-------|------------|---|-------|----------------|---|-------|----------------|-------------------------|-------|----------------|
| Treatments                                  | Trientine 2HCl versus no treatment  |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Time horizon                                | 15 years with a starting age of 18.37 years (Weiss 2011). The ESC noted that the time horizon, although conservative given the lifetime nature of WD, was consistent with available data.   |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Outcomes                                    | QALYs, LYs, number of liver transplants   |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Methods used to generate results            | Microsimulation model using a cohort expected value analysis  |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Health states                               | Four health states:<br>i) No transplant (on treatment)<br>ii) No transplant (off treatment)<br>iii) Had transplant<br>iv) Dead (absorbing health state)   |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Cycle length                                | 1 year  |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Transition probabilities                    | No transplant to had transplant: Weiss 2011 for trientine 2HCl (1.62%); Appenzeller-Herzog 2019 for no treatment (RR = 15.31).<br>Had transplant to death: ANZLITR for both arms (3% for hepatic and hepatic + neurological; 0% for neurological only)<br>No transplant to death: Weiss 2011 for trientine 2HCl (1.62%); Appenzeller-Herzog 2019 for no treatment (RR = 15.31)<br>Background mortality: ABS 2020<br>Treatment discontinuation: Weiss 2013 all-cause treatment discontinuation for trientine   |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Extrapolation method                        | Extrapolation was not used  |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Health related quality of life              | <table border="1"> <thead> <tr> <th>Health state</th> <th>Utility</th> <th>Source</th> </tr> </thead> <tbody> <tr> <td>Baseline (hepatic)</td> <td>0.860</td> <td>Schaefer 2016</td> </tr> <tr> <td>Baseline (hepatic + neurological)</td> <td>0.790</td> <td>Svetel 2011</td> </tr> <tr> <td>Baseline (neurological)</td> <td>0.641</td> <td>Schaefer 2016</td> </tr> <tr> <td>Trientine vs. no treatment</td> <td>0.021</td> <td>Weiss 2019</td> </tr> <tr> <td>Immunosuppression post-OLT (first year)</td> <td>0.690</td> <td>Ratcliffe 2002</td> </tr> <tr> <td>Immunosuppression post-OLT subsequent years</td> <td>0.760</td> <td>Ratcliffe 2002</td> </tr> <tr> <td>Post-transplant utility</td> <td>0.608</td> <td>Longworth 2002</td> </tr> </tbody> </table> | Health state   | Utility | Source | Baseline (hepatic) | 0.860 | Schaefer 2016 | Baseline (hepatic + neurological) | 0.790 | Svetel 2011 | Baseline (neurological) | 0.641 | Schaefer 2016 | Trientine vs. no treatment | 0.021 | Weiss 2019 | Immunosuppression post-OLT (first year) | 0.690 | Ratcliffe 2002 | Immunosuppression post-OLT subsequent years | 0.760 | Ratcliffe 2002 | Post-transplant utility | 0.608 | Longworth 2002 |
| Health state                                | Utility   | Source         |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Baseline (hepatic)                          | 0.860   | Schaefer 2016  |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Baseline (hepatic + neurological)           | 0.790   | Svetel 2011    |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Baseline (neurological)                     | 0.641   | Schaefer 2016  |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Trientine vs. no treatment                  | 0.021   | Weiss 2019     |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Immunosuppression post-OLT (first year)     | 0.690   | Ratcliffe 2002 |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Immunosuppression post-OLT subsequent years | 0.760   | Ratcliffe 2002 |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Post-transplant utility                     | 0.608   | Longworth 2002 |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |
| Discount rate                               | 5%  |                |         |        |                    |       |               |                                   |       |             |                         |       |               |                            |       |            |   |       |                |   |       |                |                         |       |                |

Source: Table 3-1, p74; Table 3-8, p89 of the submission.

2HCl = dihydrochloride; ABS = Australian Bureau of Statistics; ANZLITR = Australia and New Zealand Liver and Intestinal Transplant Registry; LY = life year; OLT = orthotopic liver transplant; QALY = quality adjusted life year; RR = relative risk

6.25 The submission provided the following diagram to set out the general structure of the model, making the point that in the hypothetical absence of trientine, the lack of pharmacological treatments leaves orthotopic liver transplant (OLT) as the only option to avoid death.

Figure 2: Model structure showing health state transition



Source: Figure 3-2 p75 of the submission.

- 6.26 Patients entered the model at the time of diagnosis and were placed in separate cohorts based on the presentation of hepatic (56.4%), neurological (27.9%), or hepatic + neurological (15.8%) symptoms. As such, the model included only symptomatic patients, which may not correspond to the requested restriction which does not specify that patients must be symptomatic. The PSCR stated that including an estimation of the transition from asymptomatic/pre-symptomatic WD to symptomatic WD would introduce further uncertainty into the model.
- 6.27 Liver transplant was included in the model and re-transplant was allowed for at a rate of 1.136 (Guillaud 2014). It was assumed that all patients with hepatic or hepatic + neurological symptoms were candidates for liver transplant, but patients with neurological symptoms only were not. In each cycle of the model patients had a chance of receiving a liver transplant, death, or survival without transplant. Patients in the trientine arm also had a chance of discontinuing treatment in each cycle. Once a patient received a liver transplant, they were assumed to require lifelong immunosuppression and they could only persist in that health state or die. Patients in the trientine 2HCl arm with hepatic symptoms ceased treatment if they had a transplant and were considered cured of WD, while those with hepatic + neurological symptoms continued trientine 2HCl treatment following transplant.
- 6.28 Transitions between the model health states were based on data from: i) Weiss 2011, which was not included in the clinical evidence presented, although the publication included many of the same patients that were included in Weiss 2013; ii) Appenzeller-Herzog 2019, which presented a meta-analysis of older case studies; and iii) the Australia and New Zealand Liver and Intestinal Transplant Registry (ANZLITR). Treatment discontinuation was sourced from Weiss 2013.

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Table 9: Key drivers of the model

| Description          | Method/Value   | Impact  |
|----------------------|--|---|
|                      |  | Base case ICER = ██████ <sup>1</sup> /QALY  |
| Clinical evidence    | The overall poor quality of the studies presented did not provide a basis for a quantitative estimate of effect size for trientine versus no active treatment. Therefore, the accuracy of the modelled economic evaluation is limited.   | High: favours trientine 2HCl  |
| Trientine 2HCl price | As discussed in paragraph 3.2, the requested DPMQ for trientine 2HCl is high (\$█████).  | High: arbitrarily reducing the DPMQ of trientine 2HCl to \$█████ reduced the ICER to ██████ <sup>2</sup> /QALY.   |
| Trientine 2HCl dose  | The assumed dose (1,005.7 mg/day) was based on Weiss 2018. The Weiss 2018 cohort included 20.8% patients aged <18 years and therefore the dose used in Weiss 2018 may not be representative of the dose that would be used in adult patients, which comprised the patient population in the model. | High: decreasing the dose by 10% to 905.1 mg/day reduced the ICER to ██████ <sup>3</sup> /QALY; increasing the dose by 10% to 1,106 mg/day increased the ICER to ██████ <sup>4</sup> /QALY. |

Source: Compiled during the evaluation.

2HCl = dihydrochloride; DPMQ = dispensed price for maximum quantity; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$45,000 to < \$55,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$75,000 to < \$95,000

6.29 The submission did not provide a stepped economic evaluation. The submission provided results for incremental cost per life year (LY) and quality adjusted life year (QALY) gained.

Table 10: Results of the economic evaluation

| Component   | Trientine 2HCl | No treatment | Increment          |
|---|----------------|--------------|--------------------|
| <b>Total cohort – price offered in submission (DPMQ = \$█████)</b>                |                |              |                    |
| Costs (\$)  | █████          | \$161,481    | █████              |
| OLTs avoided  | 0.141          | 0.660        | 0.519              |
| Incremental cost/OLT avoided (base case) (\$)                                     |                |              | █████              |
| LY  | 10.212         | 7.558        | 2.654              |
| Incremental cost/extra LY gained (base case) (\$)                                 |                |              | █████              |
| QALY  | 8.100          | 5.673        | 2.427              |
| Incremental cost/extra QALY gained (base case)                                    |                |              | █████ <sup>1</sup> |
| <b>Total cohort – updated price offered in pre-PBAC response (DPMQ = \$█████)</b> |                |              |                    |
| Costs (\$)  | █████          | \$161,481    | █████              |
| OLTs avoided  | 0.141          | 0.660        | 0.519              |
| Incremental cost/OLT avoided (base case) (\$)                                     |                |              | █████              |
| LY  | 10.212         | 7.558        | 2.654              |
| Incremental cost/extra LY gained (base case) (\$)                                 |                |              | █████              |
| QALY  | 8.100          | 5.673        | 2.427              |
| Incremental cost/extra QALY gained (base case)                                    |                |              | █████ <sup>2</sup> |

Source: Table 3-13, p97-98 of the submission

2HCl = dihydrochloride; LY = life year; OLT = orthotopic liver transplant; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$45,000 to < \$55,000

6.30 The base case ICER was \$55,000 to < \$75,000 per QALY. The results were generated in the absence of a quantitative estimate of effect size in the available literature.

Table 11: Results of sensitivity analyses

| Analyses  | Incremental cost (\$) | Incremental QALY | ICER             | % change ICER      |
|---|-----------------------|------------------|------------------|--------------------|
| <b>Base case</b>  | █                     | 2.427            | █ <sup>1</sup>   | -                  |
| Discount rate   |                       |                  |                  |                    |
| 3.5%  | █                     | 2.71             | █ <sup>1</sup>   | +1.4%              |
| 0%  | █                     | 3.58             | █ <sup>a,1</sup> | +4.2% <sup>a</sup> |
| Time horizon (base case: 15 years)  |                       |                  |                  |                    |
| 10 years  | █                     | 1.67             | █ <sup>1</sup>   | -5.2%              |
| 30 years  | █                     | 3.76             | █ <sup>1</sup>   | -1.2%              |
| Proportion receiving OLT vs. death (base case: 97%)                       |                       |                  |                  |                    |
| 80%   | █                     | 3.02             | █ <sup>1</sup>   | -7.8%              |
| 0%  | █                     | 5.33             | █ <sup>1</sup>   | -21.0%             |
| Relative risk OLT/death for no treatment vs. trientine (base case: 15.31) |                       |                  |                  |                    |
| 17.02   | █                     | 2.50             | █ <sup>1</sup>   | -5.3%              |
| 11.53   | █                     | 2.10             | █ <sup>2</sup>   | +22.5%             |
| Trientine 2HCl dose (base case: 1,005.7 mg/day)                           |                       |                  |                  |                    |
| 905.1 mg/day (10% decrease)   | █                     | 2.43             | █ <sup>1</sup>   | -17.3%             |
| 1,106.3 mg/day (10% increase)   | █                     | 2.43             | █ <sup>2</sup>   | +17.3%             |
| Number of transplants per OLT (base case: 1.136)                          |                       |                  |                  |                    |
| 1.0   | █                     | 2.43             | █ <sup>2</sup>   | +7.9%              |
| Price of trientine 2HCl (base case: \$ █)                                 |                       |                  |                  |                    |
| \$ █ (NSW hospital formulary price)                                       | █                     | 2.43             | █ <sup>2</sup>   | +18%               |
| \$ █  | █                     | 2.43             | █ <sup>3</sup>   | -34%               |
| \$ █  | █                     | 2.43             | █ <sup>4</sup>   | -52%               |
| \$ █  | █                     | 2.43             | █ <sup>5</sup>   | -69%               |

Source: Table 3-15, p100 of the submission; TreeAge model 'Waymade – Trientine PBAC Submission July\_S3 CEM\_Final.

2HCl = tetrahydrochloride; ICER = incremental cost effectiveness ratio; OLT = orthotopic liver transplant; QALY = quality adjusted life year; WD = Wilson disease

<sup>a</sup> Table 3-15 of the submission reported the ICER/QALY for a discount rate of 0% for cost and benefits to be █<sup>1</sup> (a change of +1.8%) however this appears to be an error as it matched another sensitivity analysis reported in Table 3-15 for the proportion of patients receiving OLT vs. death of 100%, which did result in an ICER/QALY of █<sup>1</sup>.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$45,000 to < \$55,000

<sup>4</sup> \$25,000 to < \$35,000

<sup>5</sup> \$15,000 to < \$25,000

6.31 The ESC noted that the model was highly sensitive to the DPMQ of trientine 2HCl applied. Arbitrarily applying a DPMQ of \$ █ for trientine 2HCl reduced the ICER by 34% to \$45,000 to < \$55,000 per QALY.

6.32 The model showed sensitivity to trientine 2HCl dose. This was likely to be of some relevance, as the dose used in the model (1,005.7 mg/day) was based on Weiss 2018, a cohort in which 20% of patients were less than 18 years of age, whereas the model included only adult patients. 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 paediatric patients, and the mean daily dose was sourced from Weiss 2018 which also included a mix of adult and paediatric patients and therefore, the model reflected the costs and outcomes of the total PBS population.

- 6.33 The model also showed considerable sensitivity to the relative risk applied to OLT/death for the no treatment arm. The submission attributed this to the likelihood that a high rate of transplant would be observed when no alternative pharmacological treatment is available.

### **Drug cost/patient/year**

**Table 12: Cost per patient for trientine 2HCl**

|                           | Trientine |              |                        | Total    |
|---------------------------|-----------|--------------|------------------------|----------|
|                           | Hepatic   | Neurological | Hepatic + neurological |          |
| Time on treatment (years) | 4.280     | 2.416        | 1.360                  | 8.056    |
| Cost of treatment (\$)    | ████████  | ████████     | ████████               | ████████ |
| Cost per year (\$)        | ████████  | ████████     | ████████               | ████████ |

Source: Table 3-12, p97 of the submission.  
2HCl = dihydrochloride

- 6.34 The cost of drug treatment per treatment course, estimated by the model, of 8.056 years was \$████████ for the trientine arm compared to no treatment, resulting in an incremental cost per year of \$████████.
- 6.35 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**

- 6.36 This submission was considered by DUSC. The submission applied an epidemiological approach to estimate the number of patients eligible for treatment with trientine 2HCl. 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   |
|----------------------------------|---|
| <b>Epidemiology</b>              |   |
| Prevalence data                  | Australian population: ABS 3222.0 Series B<br>Prevalence of WD: 1/30,000; source cited as Department of Health, State Government of Victoria.   |
| Eligible patients                | Prevalent patients were included in Year 1 only and estimated incident patients were considered in Years 2 to 6. The number of incident patients was estimated as the yearly increase in prevalent patients, 13-14 per year |
|                                  |   |
|                                  |   |
|                                  |   |
|                                  |   |
|                                  |   |
|                                  |   |
| <b>Utilisation</b>               |   |
| Uptake rate                      | Sponsor assumption: %.  |
|                                  |   |
|                                  |   |
|                                  |   |
|                                  |   |
|                                  |   |
|                                  |   |
| Treatment duration               | 8 years   |
| Compliance                       | 100%  |
| Number of scripts                | Trientine 2HCl: 4.02 capsules/day; 7.34 scripts/years   |
|                                  |   |
|                                  |   |
|                                  |   |
| <b>Cost of medicines</b>         |   |
| Trientine 2HCl                   | Requested price: \$   |
| Patient co-payment               | Co-payment calculated as \$20.10 for PBS and \$3.52 for RPBS.   |
| <b>Impact on other medicines</b> |   |
| Other agents                     | None.   |
| <b>MBS usage and costs</b>       |   |
| MBS items                        | None.   |

Source: Table 4-3, p104; Table 4-4, p104; Table 4-5, p105; Table 4-7, p105 of the submission.

2HCl = dihydrochloride; ABS = Australian Bureau of Statistics; DPA = penicillamine; trt = treatment; WD = Wilson disease

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

6.37 The estimated patient numbers, prescription numbers and costs for the PBS listing of trientine 2HCl 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         |
|---|----------------|----------------|----------------|----------------|----------------|----------------|
| <b>Estimated extent of use</b>                            |                |                |                |                |                |                |
| Number of patients treated <sup>a</sup>                   | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> |
| Number of scripts dispensed <sup>b</sup>                  | █ <sup>2</sup> | █ <sup>2</sup> | █ <sup>2</sup> | █ <sup>2</sup> | █ <sup>2</sup> | █ <sup>2</sup> |
| <b>Estimated financial implications of trientine 2HCl</b> |                |                |                |                |                |                |
| Cost to PBS/RPBS less copayments                          | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> |
| <b>Net financial implications</b>                         |                |                |                |                |                |                |
| Net cost to PBS/RPBS                                      | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> | █ <sup>3</sup> |

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

2HCl = dihydrochloride

<sup>a</sup> Rounded values.

<sup>b</sup> Assuming 4.02 capsules per day; 7.34 scripts/year, as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

6.38 The total cost to the PBS/RPBS of listing trientine 2HCl was estimated to be \$0 to < \$10 million in Year 6, and a total of \$40 million to < \$50 million over the first 6 years of listing. The DUSC noted that the utilisation estimates were largely influenced by the assumed proportion of patients intolerant to DPA (25%), the assumed dose (1,005.7 mg/day) and the assumed uptake rate (█%).

6.39 The dose per day was sourced from Weiss 2018. While the patient population in Weiss 2018 was similar to the proposed PBS population in that patients had discontinued DPA treatment, the submission provided no discussion as to whether the Weiss 2018 population would be similar to the likely Australian population with regard to the proportion of patients who were children. In Weiss 2018, 21% of patients were less than 18 years of age, and this would impact dosage, with the recommended dose for children being weight-based (20 mg/kg/day). As noted above (paragraph 6.32), the pre-PBAC response stated that Weiss 2018 included both adult and paediatric patients. The DUSC also noted that there was a potential for use beyond the proposed restriction into the first line population and to patients with neurological deterioration misinterpreted for DPA intolerance rather than disease progression.

### Financial Management – Risk Sharing Arrangements

6.40 No risk-sharing arrangement (RSA) was proposed. A RSA may be required given the dose used in the economic model and financial estimates was based on Weiss 2018 and may not represent use in clinical practice. In addition, the results of the financial impact sensitivity analyses indicated that there was potential for considerable alteration in the estimated net cost. It would be reasonable to consider a RSA to minimise the utilisation uncertainties that may be observed in clinical practice.

6.41 Finally, there is potential for use beyond the requested listing.

6.42 The PSCR stated that the risk of an uncertain dose and/or risk of leakage into the first line was not sufficient to warrant a RSA. The ESC considered that a RSA based on an

appropriate DPMQ and usage estimates for trientine 2HCl would be required to minimise 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 dihydrochloride (2HCl) 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 2HCl and the nomination of no active treatment 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 2HCl with no active treatment 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 2HCl 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)<sup>3</sup>, 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 no active treatment 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 2HCl 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 three observational studies evaluating DPA and trientine 2HCl and a meta-analysis of four observational studies comparing chelation therapy versus best supportive care. The PBAC considered that the quality of the evidence presented was poor and that risk of bias was high in all the presented studies.
- 7.5 The PBAC noted that these studies were used to inform a 2-step indirect treatment comparison, which firstly compared trientine 2HCl to DPA and then compared

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<sup>3</sup> 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

chelation therapy, which consisted of DPA only, to best supportive care.

- 7.6 The PBAC noted that the submission claimed that trientine 2HCl was non-inferior to DPA in terms of effectiveness and superior in terms of safety compared to DPA. 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 2HCl and DPA in terms of similarity or difference. However, the PBAC considered that the claim that trientine 2HCl and DPA were non-inferior in terms of comparative effectiveness was consistent with the accepted clinical approach to treatment and the available guidelines. The PBAC considered that it was likely that trientine 2HCl was superior compared to DPA in terms of safety, but this was poorly supported by the evidence presented.
- 7.7 The PBAC considered that the claim that chelation therapy, and thus trientine 2HCl, was superior to no active treatment in terms of efficacy and safety 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 reiterated that the most informative comparison was between trientine 2HCl and DPA.
- 7.8 The PBAC noted that the submission presented a cost-utility analysis comparing trientine 2HCl with no treatment. 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 2HCl versus no active treatment, the underlying clinical data that supported most of the input parameters was of a poor quality and the model did not include asymptomatic patients.
- 7.9 The PBAC also noted that the economic model was highly sensitive to both the dose and the price of trientine 2HCl applied in the model.
- 7.10 Noting the available guidelines and the claim in the submission that trientine 2HCl was non-inferior to DPA, the PBAC considered that the economic model was uninformative and that the substantially higher price requested for trientine 2HCl 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.
- 7.11 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 noted that the estimates were sensitive to the assumed proportion of DPA intolerant patients, the assumed dose and the assumed uptake rates. Overall, the PBAC considered that the estimates were high, primarily due to the price of trientine 2HCl requested.
- 7.12 The PBAC considered that if trientine 2HCl was cost minimised to DPA a risk sharing

arrangement would not be required.

- 7.13 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for trientine 2HCl 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.
- 7.14 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.
- 7.15 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**

The sponsor had no comment.