An addendum to this Public Summary Document has been included at the end of the document.

7.19 TRIENTINE, Tablet 150 mg (as tetrahydrochloride), Cuprior®, Orphalan

1 Purpose

1.1 The early re-entry resubmission sought to list trientine tetrahydrochloride (trientine 4HCl) for the treatment of patients with Wilson Disease (WD) who are intolerant of D-penicillamine/penicillamine (DPA).

1.2 A summary of the key matters to be addressed in a resubmission, as identified by the PBAC in its consideration of the November 2021 submission, and the approach taken in the resubmission, is presented in Table 1.

Table 1: Summary of key matters to be addressed

Matter of concern	Resubmission	Addressed?
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 and the appropriate comparator was DPA (not BSC) (para 7.3, trientine 4HCl Public Summary Document [PSD], Nov 2021).	The resubmission did not adopt the PBAC's advice regarding the proposed place in therapy or the appropriate comparator, arguing that trientine 4HCl is TGA registered for use in patients who are intolerant to DPA. The proposed restriction was revised to specify the side effects and AEs to DPA that may qualify a patient for treatment with trientine 4HCl.	No
The results of the CUA were highly uncertain (para 7.9, trientine Public Summary Document [PSD], Nov 2021). The PBAC considered that the economic evaluation should be based on a CMA versus DPA (para 7.14, trientine 4HCl PSD, Nov 2021).	No changes were made to the model. The resubmission attempted to address the uncertainties via a 17.6% reduction in the effective AEMP of trientine 4HCl from $[redacted] to $[redacted].	No
Updated utilisation and financial estimates to align with the revised place in therapy (para 7.14, trientine 4HCl PSD, Nov 2021).	The financial estimates were updated to reflect the revised AEMP only. No other changes were made. A RSA was proposed with expenditure caps set below the estimated cost to the PBS/RPBS. For use beyond the caps, a rebate of [redacted]% would be applied.	No

Source: Table 1, p9-10 of the resubmission and Trientine 4HCl November 2021 PBAC PSD

4HCl = tetrahydrochloride; AEMP = approved ex-manufacturer price; BSC = best supportive care; CMA = cost-minimisation analysis; CUA = cost-utility analysis; DPA = D-penicillamine; PBAC = Pharmaceutical Benefits Advisory Committee; RSA = risk sharing arrangement; TGA = Therapeutic Goods Administration

2 Background

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 This is the second PBAC consideration for trientine 4HCl for the treatment of WD.

2.3 In November 2021, the PBAC accepted that chelation therapy prevents the progression of WD; however, considered that the proposed place in therapy for trientine 4HCl and the nomination of best supportive care (BSC) as the comparator 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 (paragraph 7.1, trientine 4HCl Public Summary Document (PSD), November 2021).

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The requested listing, with changes suggested by the Secretariat (additions in italics, deletions in strikethrough) is presented below.

MEDICINAL PRODUCT **Medicinal product pack**	**PBS item code**	**Max. qty (packs)**	**Max. qty (units)**	**No. of repeats**	**DPMQ**	**Available brands**
TRIENTINE						
trientine tetrahydrochloride, 150 mg tablet, 72	NEW	2	144	5	Published: $7,441.22 Effective: $[redacted]	Cuprior
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: ☒Medical Practitioners						
Restriction type: ☒Authority Required *(telephone/online PBS Authorities system)*						
Episodicity: ~~Chronic~~						
Severity: [blank]						
Condition: ~~Wilson's disease~~ *Chelation of elevated copper levels*						
Indication: ~~Wilson's disease~~ *Chelation of elevated copper levels*						
Treatment Phase: ~~Initial PBS subsidised treatment~~						
Clinical criteria:						
Patient must have a diagnosis of Wilson disease that is either: (i) established, (ii) possible, but then which has been subsequently confirmed through further diagnostic tests, as defined by the Wilson disease scoring system (Leipzig score) developed by the European Association for Study of Liver (see NOTE for further details)						
Alternative for CC1 *The condition must be proven to be Wilson disease through genetic variations/abnormalities in the ATP7B gene, once only prior to initiating treatment with this drug*						
AND						
Clinical criteria:						
Patient must be intolerant to ~~treatment with~~ ~~D~~-penicillamine						
~~**Clinical**~~ ***Population*** **criteria:**						
Patient ~~requires copper chelation therapy~~ *must have Wilson disease*						
AND						

Population criteria:
Patient must be ~~aged~~ *at least* 5 years ~~or older~~ *of age*
Treatment criteria:
Must be treated by *at least one of the following, where this authority application is to initiate treatment with this drug:* ~~a~~ *(i)* gastroenterologist, *(ii)* hepatologist, ~~or~~ *(iii)* neurologist*; the authority prescription must contain the specialist prescriber's details; or*
Must be treated by a medical practitioner of any type, where this authority application is continuing established treatment initiated by one of the above mentioned specialist types.
Prescribing 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)~~ *Prior to seeking this authority, establish evidence of excess copper levels based on at least one of: (i) clinical symptoms, (ii) measured serum copper levels, (iii) measured urinary copper levels.* *Document what these findings were in the patient's medical records. Do not supply them in this authority application.*
Prescribing instructions: *Refer to the following definitions if in doubt over what constitutes an acceptable intolerance to penicillamine:* *Side effects of penicillamine occurring soon after initiation (within first few weeks/months):* *(i) fever, (ii) rash, (iii) enlarged lymph nodes, (iv) neutropenia, (v) thrombocytopenia, (vi) proteinuria, (vii) severe, persistent nausea.* *Side effects of penicillamine developing later:* *(i) nephrotic syndrome, (ii) glomerulonephritis, (iii) total bone marrow aplasia, (iv) skin changes (cutis laxa, elastosis perforans serpiginosa, pemphigus), (v) myasthenia gravis, (vi) polymyositis, (vii) Goodpasture syndrome, (viii) optic neuritis, (ix) proteinuria (1-2 gm/day or equivalent in children, depending on specialist Wilson disease and renal review), (x) haematuria (if cause unknown), (xi) thrombocytopenia/leukopenia, (xii) bleeding related to thromobocytopenia/leukopenia, (xiii) lupus-like syndrome (haematuria, proteinuria, positive antinuclear antibody), (xiv) arthralgia.*
Prescribing instructions: ~~Patients are considered intolerant to D-penicillamine if they develop one or more side effects during a relevant period of use which is of a severity to necessitate treatment withdrawal. Details of the specific toxicity experienced by the patient must be provided at the time of application.~~ *At the time of the first authority application for this drug, document the details (date of reaction, severity of reaction, dose of penicillamine, etc) of the penicillamine intolerance, if not already done, in the patient's medical records. Do not supply these details in this authority application.*
Administrative Advice: *The Wilson disease scoring system referenced in this listing is the scoring system described in the European Association for Study of Liver (EASL) Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012 Mar; 56(3):671-85.* *The following website provides an online calculator for the scoring system:* *https://gastroliver.medicine.ufl.edu/hepatology/for-physicians/wilsons-disease-scoring-system* *The Australian Government is not the website owner of this online calculator and takes no responsibility for its accuracy, functionality or updating of the information contained within.*
Administrative Advice: *Special Pricing Arrangements apply*
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

3.2 The resubmission requested a special pricing arrangement, with an effective approved ex-manufacturer price (AEMP) of $. This represents a 17.6% reduction to the effective AEMP offered in the November 2021 submission.

3.3 The resubmission proposed a revised restriction which limited use to patients aged 5 years and older to align with the TGA indication.

3.4 The resubmission also proposed documentation of the specific DPA-related intolerance that qualified a patient for treatment with trientine 4HCl. The resubmission provided examples of adverse events to DPA that commonly lead to discontinuation as outlined in the UK Clinical Commissioning Policy for trientine, developed by the NHS. This document specifies the side effects to DPA that may qualify a patient with WD for treatment with trientine, reflecting adverse reactions reported in the literature and Product Information that would pose too much of a safety concern to continue DPA use of significantly impact a patients' willingness to continue treatment. The Secretariat proposed including the adverse events that commonly lead to the discontinuation of DPA in the trientine 4HCl restriction as a prescribing instruction. The pre-PBAC response considered the additions to the restriction were reasonable.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Comparative effectiveness

4.3 The November 2021 consideration was based on a two-step indirect comparison of trientine 4HCl versus BSC, targeting the patient population who were intolerant of DPA. The evidence provided in the original 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 dihydrochloride) 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.

4.4 The PBAC considered that the quality of the evidence presented was poor and that risk of bias was high in all the presented studies (paragraph 7.5, trientine 4HCl PSD, November 2021).

4.5 The PBAC considered that the claim that chelation therapy, and thus trientine 4HCl, 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 (paragraph 7.8, trientine 4HCl PSD, November 2021).

4.6 The resubmission accepted that the quality of the evidence presented was of poor quality and aimed to address PBAC's uncertainties about the effectiveness through the 17.6% reduction to the effective approved ex-manufacturer price (AEMP) and the proposed RSA.

4.7 No additional clinical data were presented in the resubmission.

Economic analysis

4.8 A summary of the key matters to be addressed is presented in **Error! Reference source not found.**.

Table 2: Summary of key matters to be addressed – economic model

Matter of concern	Resubmission	Addressed?
The PBAC considered that the results of the CUA between trientine 4HCl and BSC were highly uncertain as the studies 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 (para 7.9, trientine 4HCl PSD, Nov 2021). The PBAC considered that an economic evaluation based on a CMA versus DPA would be appropriate (para 7.14, trientine 4HCl PSD, Nov 2021).	No changes were made to the model structure. The resubmission attempted to address the PBAC's concern of uncertainty through a 17.6% reduction in the effective AEMP of trientine 4HCl offered (from $[redacted] to $[redacted]) (this was the only input changed in the resubmission). Sensitivity analyses were presented that included the costs and outcomes of liver transplant.	No
Base case ICER = $[redacted][2] per QALY	Revised base-case ICER = $[redacted][1] per QALY	-

Source: Table 1, pp9-10 of the resubmission and Trientine 4HCl PSD, November 2021

4HCl = tetrahydrochloride; AEMP = approved ex-manufacturer price; BSC = best supportive care; CMA = cost-minimisation analysis; CUA = cost-utility analysis; DPA = D-penicillamine; ICER = incremental cost effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year; RSA = risk sharing arrangement

The redacted values correspond to the following ranges:

[1] *$95,000 to < $115,000*

[2] *$135,000 to < $155,000*

4.9 The resubmission re-presented the cost-utility analysis of trientine 4HCl versus 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.

4.10 The only change made to the model was to the effective AEMP of trientine 4HCl, which was reduced from $ to $ (effective dispensed price per maximum quantity (DPMQ) reduced from $ to $).

4.11 The results of the economic evaluation are presented in **Error! Reference source not found.**.

Table 3: Results of the economic evaluation (discounted)

	Trientine 4HCl	BSC	Increment
March 2022 early re-entry resubmission			
Costs	$	$	$
LYs	17.558	6.946	10.612
QALYs	14.984	4.515	10.469
Incremental cost per QALY gained			**$**[1]
November 2021 submission			
Costs	$	$	$
LYs	17.558	6.946	10.612
QALYs	14.984	4.515	10.469
Incremental cost per QALY gained			**$**[2]

Source: Table 7, p22 of the resubmission and Table 8, p16 of the trientine 4HCl PSD, November 2021
4HCl = tetrahydrochloride; BSC = best supportive care; LY = life year; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1]*$95,000 to < $115,000*
[2]*$135,000 to < $155,000*

4.12 A sensitivity analysis was presented in the resubmission that incorporated the implications of setting the proposed RSA expenditure caps below the estimated PBS/RPBS costs. The submission stated that the RSA could be expected to reduce the effective AEMP to approximately $. This would require considerable use beyond the proposed expenditure caps. If the caps were reached for the entire 6-year period, the effective AEMP would be reduced to approximately $.

Table 4: Results of sensitivity analyses that incorporated a reduced effective AEMP for trientine 4HCl

	Trientine 4HCl	BSC	Increment
AEMP of trientine 4HCl = $			
Costs	$	$	$
LYs	17.558	6.946	10.612
QALYs	14.984	4.515	10.469
Incremental cost per QALY gained			**$**[1]
AEMP of trientine 4HCl = $			
Costs	$	$	$
LYs	17.558	6.946	10.612
QALYs	14.984	4.515	10.469
Incremental cost per QALY gained			**$**[1]

Source: Table 7, p22 of the resubmission and Section 3_CEA_Cuprior_ERE.xlsx
4HCl = tetrahydrochloride; AEMP = approved ex-manufacturer price; BSC = best supportive care; LY = life year; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1]*$75,000 to < $95,000*

Drug cost/patient/year

Table 5: Drug cost per patient per year for trientine 4HCl

	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 =	$	
November 2021		$	
Treatment cost – financial estimates			
DPMQ	Resubmission assumes 4.14 tablets per day (included paediatric patients)	$	Not included
Cost/year	$ × 12 =	$	
November 2021		$	

Source: calculated during evaluation
4HCl=tetrahydrochloride; BSC=best supportive care; DPMQ = dispensed price for maximum quantity; WD = Wilson Disease

4.13 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 utilisation and financial implications

4.14 A summary of the key matters to be addressed is presented in Table 66.

Table 6: Summary of key matters to be addressed – financial implications

Matter of concern	Resubmission	Addressed?
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 estimates were sensitive to the assumed dose and the proportion of adult and paediatric patients. Overall, financial estimates were high, primarily due to the price of trientine 4HCl (para 7.12, trientine 4HCl PSD, Nov 2021). The PBAC recommended that the utilisation and financial estimated be updated to align with the revised place in therapy (para 7.14, trientine 4HCl PSD, Nov 2021).	Data on the number of patients accessing DPA from DUSC were used to provide certainty around the expected utilisation of trientine 4HCl. The only change to the financial estimate calculations was the inclusion of the 17.6% reduction to the effective AEMP. The resubmission also presented a RSA which consisted of expenditure caps set below the estimated cost to the PBS/RPBS, beyond which a [redacted]% rebate would be applied.	No

Source: Table 1, pp9-10 of the resubmission and Trientine 4HCl November 2021 PBAC PSD
4HCl = tetrahydrochloride; AEMP = approved ex-manufacturer price; DPA = D=penicillamine; DUSC = Drug Utilisation Sub-Committee; PBAC = Pharmaceutical Benefits Advisory Committee; RSA = risk sharing arrangement

4.15 The resubmission presented data provided by the DUSC Secretariat on the utilisation of DPA in Australian clinical practice from 1 January 2016 to 31 October 2021. This data demonstrated that the number of prevalent DPA patients had been declining slowly since 2019, with 471 prevalent patients in 2020 (including 62 incident patients). The resubmission did not provide any reasoning as to why the number of prevalent

DPA patients has been declining since 2019, which may have been due to the increased availability of trientine.

4.16 The resubmission noted that the November 2021 submission estimated that approximately 310 patients would be treated with DPA in Year 1 (2022). The resubmission stated that this demonstrated that the utilisation of trientine was underestimated. Compared to the data provided by the DUSC Secretariat, it appeared that number of patients treated with DPA was underestimated in both the original submission and the resubmission.

4.17 The resubmission, like the November 2021 submission, stated that 30% of patients would be intolerant to DPA (Ferenci 2012, Socha 2018, Weiss 2013) and then assumed that uptake amongst these patients would be 80% in Year 1, increasing to 90% in Year 6.

4.18 The only change to the financial estimates provided in the resubmission was the inclusion of the 17.6% reduction to the effective AEMP.

4.19 The estimated net financial impact to the PBS/RPBS for the listing of trientine 4HCl based on the proposed effective price is $20 million to < $30 million over the first six years of listing (Table 7). In November 2021, the estimated net impact was $30 million to < $40 million over the first six years of listing.

Table 7: Estimated utilisation and cost of trientine 4HCl (effective price)

	Year 1 - 2022	Year 2 - 2023	Year 3 - 2024	Year 4 - 2025	Year 5 - 2026	Year 6 - 2027
DPA-experienced patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
% DPA-intolerant	30%					
Trientine 4HCl eligible patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Uptake	80%	82%	84%	86%	88%	90%
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patient years of treatment (inclusive of discontinuations)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Script volume[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Less patient co-payments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
November 2021 submission						
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Table 11, p27 of the resubmission, Section 4_BIM_Cuprior_ERE.xlsx and Table 14, p21 Trientine 4HCl PSD, November 2021
4HCl = tetrahydrochloride; DPA = D-penicillamine; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
a. Resubmission assumed 12 prescriptions per patient year of treatment
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$0 to < $10 million*

4.20 In the RSA proposed by the resubmission, the cost to the PBS/RPBS (including co-payments) was reduced over the forward estimates (from 100% of the total estimate in Year 1 to 80% of the total estimate in Year 6). The patient co-payments were then subtracted to give the proposed RSA expenditure caps.

4.21 Use of trientine 4HCl beyond the expenditure caps would be subject to a [redacted]% rebate, which would make the cost of trientine 4HCl equivalent to the cost of DPA. This was based on an annual cost of DPA of $[redacted] and for trientine 4HCl of $[redacted].

Table 8: Calculation of the proposed expenditure caps for trientine 4HCl

	Year 1 - 2022	Year 2 - 2023	Year 3 - 2024	Year 4 - 2025	Year 5 - 2026	Year 6 - 2027
Cost to PBS/RPBS (including co-pay)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Total cost to PBS/RPBS	$[redacted][2]					
Expenditure cap levels	100.0%	95.0%	90.0%	85.0%	82.5%	80.0%
Expenditure caps	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Total expenditure	$[redacted][2]					
Patient co-payments	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Proposed PBS/RPBS expenditure caps	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Total PBS/RPBS expenditure	$[redacted][2]					

Source: Table 11, p27 of the resubmission

4HCl = tetrahydrochloride; co-pay = co-payment; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

[1] $0 to < $10 million

[2] $20 million to < $30 million

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC did not recommend trientine tetrahydrochloride (4HCl) for the treatment of patients with Wilson disease (WD) who are intolerant to penicillamine/D-penicillamine (DPA). The PBAC noted that the only changes in the resubmission were a small price reduction for trientine 4HCl and a proposed risk sharing arrangement (RSA). The PBAC therefore considered that the economic analysis remained uninformative, and the price differential compared to DPA was not justified, even with a second-line listing for trientine 4HCl, given the clinical data was more consistent with non-inferiority to DPA.

5.2 The PBAC noted that no consumer comments were received in support of the resubmission.

5.3 The PBAC noted that the resubmission again proposed that trientine 4HCl be used as a second-line treatment in patients intolerant to DPA. Although this did not align with November 2021 PBAC request that the resubmission present trientine 4HCl as line agnostic, the PBAC considered that as it aligned with the approved TGA indication it was reasonable. The PBAC therefore also considered that the nomination of best supportive care (BSC) as the comparator was reasonable.

5.4 The PBAC noted that no new clinical evidence was presented. The Committee therefore again considered that the claim that:

- trientine 4HCl was non-inferior to DPA in terms of effectiveness was consistent with the accepted clinical approach to treatment and the available guidelines, although the data presented in the November 2021 submission were of low

quality;

- trientine 4HCl was superior compared to DPA in terms of safety was likely supported, although this was poorly supported by the evidence presented in the November 2021 submission;
- chelation therapy, and thus trientine 4HCl, 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 the benefit was poorly supported by the evidence presented in the November 2021 submission; and
- trientine 4HCl was inferior in terms of safety compared to BSC could not be assessed based on the evidence presented in the November 2021 submission.

5.5 The PBAC noted that the resubmission presented the same cost-utility analysis model as in November 2021, with the only change being that the effective ex-manufacture price of trientine 4HCl was reduced by 17.6% from $ to $. The PBAC recalled that in November 2021 it 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 PBAC considered that as the issues from November 2021 remained, the economic evaluation was again uninformative.

5.6 The PBAC noted that the utilisation and financial impact estimates remained unchanged from the November 2021 submission, with the exception of the inclusion of the reduced effective price of trientine 4HCl. The PBAC considered that the estimates remained high and uncertain due to uncertainties surrounding the epidemiology of WD and the application of assumptions that remained unjustified and unsupported by the evidence.

5.7 Overall, the PBAC acknowledged that while it can be challenging for sponsors to be expected to price a new drug based on a comparison to old drugs for commercial reasons, the PBAC considered that the resubmission should be considered on its merits and a commercial imperative was not a valid reason to consider trientine 4HCl differently to other applications. The PBAC noted the 17.6% price reduction and the proposed RSA; however, did not consider that these changes represented a reasonable way forward.

5.8 The PBAC also noted that the approach taken in the resubmission differed from that suggested by the Committee in November 2021, which was a line agnostic listing with an economic evaluation based on a cost minimisation approach versus DPA and updated financial estimates to align with the revised place in therapy. The PBAC acknowledged that the approach adopted by the sponsor was discussed with the PBAC Chair; however, the Committee did not accept that the overall approach was reasonable given the substantially higher drug cost per patient for the same outcome compared to DPA was not justified.

5.9 The PBAC considered a resubmission for trientine 4HCl should address the

substantially higher drug cost per patient for trientine 4HCl compared to DPA, when the clinical data shows that the drugs are non-inferior in terms of efficacy, via a cost minimisation approach versus DPA. The PBAC considered that a small premium for reduced adverse events and improved tolerability versus DPA may be reasonable. The PBAC advised that revised financial estimates would also be required.

5.10 The PBAC noted that the resubmission proposed a risk sharing arrangement (RSA) in which a rebate of % was offered for use beyond the proposed expenditure caps. The PBAC considered that the proposed RSA did not compensate for the high price of trientine 4HCl. The PBAC considered that if the price was reduced as suggested in paragraph 5.9 a RSA would not be required.

5.11 A resubmission may be lodged for consideration at any future PBAC meeting in accordance with lodgement timelines applicable to a standard re-entry pathway submission for that PBAC meeting.

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

Outcome:
Not recommended

Addendum to the March 2022 PBAC PSD:

3.01 TRIENTINE, Tablet 150 mg (as tetrahydrochloride), Cuprior®, Orphalan

6 Background

6.1 At its March 2022 meeting, the PBAC did not recommend the PBS listing of trientine tetrahydrochloride (4HCl) for the treatment of patients with Wilson disease (WD) who are intolerant to penicillamine/D-penicillamine (DPA). As noted in paragraph 5.1 above, the decision to not recommend was due to the uninformative economic analysis and the large price differential compared to DPA, given that the clinical data suggested non-inferiority to DPA.

6.2 Following the March 2022 PBAC meeting, the sponsor for trientine 4HCl provided a revised pricing proposal that offered a 44.8% lower price compared with the March 2022 resubmission (revised approved ex-manufacturer price (AEMP) of $ per 144 x 150 mg tablets compared with $ in March 2022).

6.3 Incorporation of the revised AEMP into the economic model provided in the March 2022 resubmission resulted in an incremental cost effectiveness ratio (ICER) of $55,000 to < $75,000 per quality adjusted life year (QALY).

Table 9: Updated cost effectiveness results

	Trientine 4HCl	No treatment	Increment
Revised pricing proposal – AEMP = $ per 144 x 150 mg tablets			
Costs	$	$	$
QALY	14.984	4.515	10.469
Incremental cost/extra QALY gained			**$**[1]
March 2022 resubmission – AEMP = $ per 200 x 250 mg capsules			
Costs	$	$	$
QALY	14.984	4.515	10.469
Incremental cost/extra QALY gained			**$**[2]

Source: Table 21 p4 of the revised pricing proposal
4HCl = tetrahydrochloride; AEMP = approved ex-manufacturer price; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1]$55,000 to < $75,000
[2]$95,000 to < $115,000

6.4 Incorporation of the revised AEMP into the financial model provided in the March 2022 resubmission, resulted in an estimated net financial impact to the PBS/RPBS of $10 million to < $20 million over the first six years of listing (compared to $20 million to < $30 million in the March 2022 resubmission).

Table 10: Updated financial impact estimates

	2022	2023	2024	2025	2026	2027
Patients treated	[1]	[1]	[1]	[1]	[1]	[1]
Script volume[a]	[2]	[2]	[2]	[2]	[2]	[2]
Net cost to PBS/RPBS[b]	**$**[3]	**$**[3]	**$**[3]	**$**[3]	**$**[3]	**$**[3]
March 2022 resubmission						
Net cost to PBS/RPBS	**$**[3]	**$**[3]	**$**[3]	**$**[3]	**$**[3]	**$**[3]

Source: Table 2, p5 of the revised pricing proposal
a Revised pricing proposal assumed 12 prescriptions per patient year of treatment
b Net cost to PBS/RPBS differs to that in the revised pricing proposal as that cost included patient co-payments
The redacted values correspond to the following ranges:
[1]< 500
[2]500 to < 5,000
[3]$0 to < $10 million

6.5 The revised pricing proposal did not offer a risk sharing arrangement (RSA).

7 PBAC Outcome

7.1 At its May 2022 meeting, the PBAC recommended the PBS listing of trientine tetrahydrochloride (4HCl) for the treatment of patients with Wilson disease who are intolerant to penicillamine/D-penicillamine. The PBAC considered that the cost effectiveness of trientine 4HCl could be brought into an acceptable range with a reduced price.

7.2 The PBAC noted the revised pricing proposal provided by the sponsor.

7.3 The PBAC noted that, as the only change to the economic model was the incorporation of the reduced AEMP of trientine 4HCl, the issues identified previously remained and the economic evaluation was uninformative. However, given non-inferior clinical effectiveness to DPA was previously accepted, a small price premium for the second-

line treatment in patients intolerant to DPA would be acceptable. The PBAC considered that a further price reduction to the approved ex-manufacturer price (AEMP) offered in the revised pricing proposal was required.

7.4 The PBAC noted that although trientine 4HCl was not considered to be bioequivalent with other formulations (i.e. trientine 2HCl), the TGA had stated that if there was an interruption to the supply of one formulation, a patient could be switched to the alternate formulation. The PBAC recalled that the November 2021 submission stated that in terms of trientine base, 0.668 mg of trientine 4HCl was expected to be similar in effectiveness to 1 mg of trientine 2HCl. The PBAC considered, on the basis of these equi-effective doses, that the cost per patient for trientine 4HCl should be no more than the cost of trientine 2HCL, should the current near market product trientine 2HCl be PBS listed.

7.5 The PBAC, noting that a significantly reduced AEMP would mitigate the financial risk and uncertainty, considered that a risk sharing arrangement may not be required.

7.6 The PBAC recommended that the proposed restriction be amended so that the Prescribing Instruction states 'Prior to seeking the initial authority', rather than 'Prior to seeking this authority' to prevent patients having to stop/start treatment when copper levels have normalised/are elevated. The PBAC also considered that the clinical criterion 'Patient must have a diagnosis of Wilson disease' was reasonable.

7.7 Noting the advice from the TGA in paragraph 7.4, the PBAC recommended that trientine 4HCl should be treated as interchangeable on an individual patient basis with trientine 2HCl if trientine 2HCl was recommended and listed on the PBS, according to s101(3BA) of the *National Health Act 1953*.

7.8 The PBAC advised that trientine 4HCl is suitable for prescribing by nurse practitioners in the continuing phase of treatment only.

7.9 The PBAC recommended that the Early Supply Rule should apply.

7.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for trientine 4HCl:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over no active treatment;

b) The treatment is not expected to address a high an urgent unmet clinical need as alternate treatments are available; and

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.11 The PBAC noted that this submission was not eligible for an Independent Review as it is a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
TRIENTINE					
trientine tetrahydrochloride 150 mg tablet, 72	NEW	2	144	5	Cuprior
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners ☒Nurse Practitioners - CTO				
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)				
	Severity: [blank]				
	Condition: Chelation of elevated copper levels				
	Indication: Chelation of elevated copper levels				
	Clinical criteria:				
	Patient must have a diagnosis of Wilson disease				
	AND				
	Clinical criteria:				
	Patient must be intolerant to penicillamine				
	Population criteria:				
	Patient must have Wilson disease				
	Treatment criteria:				
	Must be treated by a specialist medical practitioner, where this authority application is to initiate treatment with this drug, of the following type: (i) gastroenterologist, (ii) hepatologist, (iii) neurologist; the authority prescription must contain the specialist prescriber's details; or				
	Must be treated by a medical practitioner (of any type), where this authority application is continuing established trientine treatment (of any specified salt) initiated by one of the above mentioned specialist types; or				
	Must be treated by a nurse practitioner where this authority application is continuing established trientine treatment (of any specified salt) initiated by one of the above mentioned specialist types				
	Prescribing Instructions: Prior to seeking the initial authority, establish evidence of excess copper levels based on at least one of: (i) clinical symptoms, (ii) measured serum copper levels, (iii) measured urinary copper levels. Document what these findings were in the patient's medical records. Do not supply them in this authority application.				

	Prescribing instructions: Refer to the following definitions if in doubt over what constitutes an acceptable intolerance to penicillamine: Side effects of penicillamine occurring soon after initiation (within first few weeks/months): (i) fever, (ii) rash, (iii) enlarged lymph nodes, (iv) neutropenia, (v) thrombocytopenia, (vi) proteinuria, (vii) severe, persistent nausea. Side effects of penicillamine developing later: (i) nephrotic syndrome, (ii) glomerulonephritis, (iii) total bone marrow aplasia, (iv) skin changes (cutis laxa, elastosis perforans serpiginosa, pemphigus), (v) myasthenia gravis, (vi) polymyositis, (vii) Goodpasture syndrome, (viii) optic neuritis, (ix) proteinuria (1-2 gm/day or equivalent in children, depending on specialist Wilson disease and renal review), (x) haematuria (if cause unknown), (xi) thrombocytopenia/leukopenia, (xii) bleeding related to thromobocytopenia/leukopenia, (xiii) lupus-like syndrome (haematuria, proteinuria, positive antinuclear antibody), (xiv) arthralgia.
	Prescribing Instructions: At the time of the first authority application for this drug, document the details (date of reaction, severity of reaction, dose of penicillamine, etc) of the penicillamine intolerance, if not already done, in the patient's medical records. Do not supply these details in this authority application.
	Administrative Advice: Special Pricing Arrangements apply
	Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners**.**
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.