7.20 TRIENTINE, Capsule containing trientine dihydrochloride 250 mg (equivalent to 166.7 mg trientine), Waymade®, Clinect Pty Ltd

1 Purpose

1.1 The early re-entry resubmission sought to list trientine dihydrochloride (trientine 2HCl) 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 2HCl should be line agnostic and the appropriate comparator was DPA (not no active treatment) (para 7.3, trientine 2HCl 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 2HCl is TGA registered for use in patients who are intolerant to DPA.	No
The results of the CUA were highly uncertain (para 7.8, trientine 2HCl PSD, Nov 2021). The PBAC considered that the economic evaluation should be based on a CMA versus DPA (para 7.13, trientine 2HCl PSD, Nov 2021).	No changes were made to the model structure. The resubmission attempted to address the uncertainties via a [redacted]% reduction in the effective AEMP of trientine 2HCl from $[redacted] to $[redacted].	No
Updated utilisation and financial estimates to align with the revised place in therapy (para 7.13, trientine 2HCl PSD, Nov 2021).	The financial estimates were updated to address the issues identified by the PBAC including reducing the proportion of patients who develop an intolerance to DPA and restricting the age of the prevalent population. The estimates were also updated to reflect the revised AEMP. A RSA was proposed based expenditure caps, beyond which a rebate of [redacted]% would be applied.	No

Source: Compiled during evaluation from the resubmission and Trientine 2HCl November 2021 PBAC PSD; HCl = dihydrochloride; AEMP = approved ex-manufacturer price; CMA = cost-minimisation analysis; CUA = cost-utility analysis; DPA = D-penicillamine; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; RSA = risk sharing arrangement; TGA = Therapeutic Goods Administration

2 Background

2.1 Trientine 2HCl was approved for registration by the TGA on 11 January 2021 for the treatment of Wilson's Disease in patients who are intolerant of penicillamine.

2.2 This is the second PBAC consideration for trientine 2HCl 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 2HCl and the nomination of no active treatment 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 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 (paragraph 7.1, trientine 2HCl 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 dihydrochloride, 250 mg capsule, *50*	NEW	2	100	5	Published: $[redacted] Effective: $[redacted]	Trientine Waymade
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: ☒Medical Practitioners ☒*Nurse Practitioners*						
Restriction type: ☒~~Authority Required – written~~ ☒Authority Required *(telephone/online PBS Authorities system)*						
Episodicity: ~~Chronic~~						
Severity: [blank]						
Condition: ~~Wilson's disease~~ *Chelation of elevated copper levels*						
~~**PBS**~~ **Indication:** ~~Wilson's disease~~ *Chelation of elevated copper levels*						
Treatment Phase: ~~Initial 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 ~~have trialled and have demonstrated intolerance~~ *be intolerant* to penicillamine ~~therapy~~ ~~The authority application must include:~~						

~~(i) a completed authority prescription form; and~~ ~~(ii) reports demonstrating the patient has failed treatment with penicillamine therapy, providing details of the nature and severity of the intolerance.~~
~~**Clinical**~~ ***Population*** **criteria:**
Patient ~~requires copper chelation therapy~~ *must have Wilson disease*
Treatment criteria:
Must be treated by at least one of the following, where this authority application is to initiate treatment with this drug: (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 or nurse practitioner, where this authority application is continuing established treatment initiated by one of the above mentioned specialist types.
Prescribing Instructions: *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:* *<u>Side effects of penicillamine occurring soon after initiation (within first few weeks/months):</u>* *(i) fever, (ii) rash, (iii) enlarged lymph nodes, (iv) neutropenia, (v) thrombocytopenia, (vi) proteinuria, (vii) severe, persistent nausea.* *<u>Side effects of penicillamine developing later:</u>* *(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: *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 % reduction to the effective AEMP offered in the November 2021 submission, and is equivalent to the effective AEMP offered in the November 2021 Pre-Sub-Committee Response (PSCR).

3.3 The resubmission proposed amendments to that presented in November 2021. These included that initial treatment be a in writing only type Authority Required listing, rather than telephone/online, and a criterion that the authority application must include (i) a completed authority prescription form, and (ii) reports demonstrating that the patient had failed treatment with DPA, including details of the nature and severity of the intolerance.

3.4 The resubmission also proposed that nurse practitioners are suitable prescribers for continuing patients where care is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan.

3.5 The Secretariat proposed including the adverse events that commonly lead to the discontinuation of DPA in the trientine 2HCl 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 2HCl versus no active treatment, targeting the patient population who were intolerant of DPA. The evidence provided in the original 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.

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 7.4, trientine 2HCl PSD, November 2021).

4.5 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 (paragraph 7.7, trientine 2HCl PSD, November 2021).

4.6 No additional clinical data were presented in the resubmission.

Economic analysis

4.7 A summary of the key matters to be addressed is presented in Table 2.

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 2HCl and no active treatment were highly uncertain as the studies did not provide a basis for a quantitative estimate of effective size for trientine 2HCl versus no 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 (para 7.8, trientine 2HCl PSD, Nov 2021). The PBAC considered that an economic evaluation based on a CMA versus DPA would be appropriate (para 7.13, trientine 2HCl PSD, Nov 2021).	No changes were made to the model structure. The resubmission attempted to address the PBAC's concern of uncertainty through a [redacted]% reduction in the effective AEMP of trientine 2HCl offered (from $[redacted] to $[redacted]) (this was the only input changed in the resubmission). The proposed reduction to the effective AEMP was equal to that offered in the November 2021 pre-PBAC response.	No
Base case ICER = $[redacted][2] per QALY	Revised base-case ICER = $[redacted][1] per QALY	-

Source: Section 3, p15 and Table 4.1, p21 of the resubmission and Trientine 2HCl PSD, November 2021
2HCl = dihydrochloride; AEMP = approved ex-manufacturer price; 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
The redacted values correspond to the following ranges
[1]*$45,000 to < $55,000*
[2]*$55,000 to < $75,000*

4.8 The resubmission re-presented the cost-utility analysis of trientine 2HCl versus no active treatment as the comparator on the grounds that no other pharmacological treatments are available for patients with WD who are intolerant of DPA.

4.9 The only change made to the model was to the effective AEMP of trientine 2HCl, which was reduced from $[redacted] to $[redacted] (effective dispensed price per maximum quantity (DPMQ) reduced from $[redacted] to $[redacted]).

4.10 The results of the economic evaluation are presented in Table 3.

Table 3: Results of the economic evaluation (discounted)

	Trientine 2HCl	No active treatment	Increment
March 2022 early re-entry resubmission			
Costs	$	$	$
LYs	10.212	7.558	2.654
QALYs	8.100	5.673	2.427
Incremental cost per QALY gained			**$**[1]
November 2021 submission			
Costs	$	$	$
LYs	10.212	7.558	2.654
QALYs	8.100	5.673	2.427
Incremental cost per QALY gained			**$**[2]

Source: Table 3.1, p15 of the resubmission
2HCl = dihydrochloride; LY = life year; QALY = quality adjusted life year
The redacted values correspond to the following ranges
[1]*$45,000 to < $55,000*
[2]*$55,000 to < $75,000*

Drug cost/patient/year

Table 4: Drug cost per patient per year for trientine 2HCl

	Trientine 2HCl
Time on treatment (years)	8.056
Cost of treatment	$
Cost per year	$
Cost per year November 2021 submission	$

Source: Calculated during evaluation
2HCl = dihydrochloride

4.11 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

4.12 A summary of the key matters to be addressed is presented in Table 5.

Table 5: 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 the modelling assumptions were not well justified. The PBAC noted that the estimates were sensitive to the assumed proportion of DPA intolerant patients, the assumed dose and assumed uptake rates. The PBAC considered that the financial estimates were high, primarily due to the price of trientine 2HCl (para 7.11, trientine 2HCl PSD, Nov 2021). The PBAC recommended that the utilisation and financial estimated be updated to align with the revised place in therapy (para 7.13, trientine 2HCl PSD, Nov 2021).	The resubmission reduced the proportion of patients who develop an intolerance to DPA from 25% to 20% to reflect a more conservative estimate. The proportion of patients who present with a neurological manifestation of WD (5.3% x 43.6% = 2.3%) was subtracted from this to result in 17.7% of patients being intolerant to DPA. The age of the prevalent population was restricted to patients ≥ 6 years. The [redacted]% reduction to the effective AEMP was included. The resubmission also proposed an RSA which consisted of expenditure caps, beyond which a [redacted]% rebate would be applied.	Partially

Source: Section 4.1, pp17-21 of the resubmission and Trientine 2HCl November 2021 PBAC PSD

2HCl = dihydrochloride; AEMP = approved ex-manufacturer price; DPA = D=penicillamine; PBAC = Pharmaceutical Benefits Advisory Committee; RSA = risk sharing arrangement; WD = Wilson disease

4.13 The table below compares the key input parameters and changes between the November 2021 submission and the March 2022 resubmission.

Table 6: Key changes to input parameters between the November 2021 and March 2022 submissions

Parameter	November 2021 submission	March 2022 resubmission
Trientine 2HCl effective AEMP	200 x 250 mg capsules = $[redacted]	200 x 250 mg capsules = $[redacted]
Trientine 2HCl effective DPMQ	$[redacted]	$[redacted]
Prevalence of WD	1 in 30,000 persons	1 in 30,000 persons aged ≥ 6 years
% intolerant to DPA	25%	20%
% DPA treated patients with neurological worsening mistaken for DPA intolerance	-	5.3%
% with neurological manifestation of WD	-	43.6%
% eligible	25%	17.7%
Uptake rate	90% all years	Unchanged
Prevalent patients*	2022: 891	2022: 823
Incident patients*	2022: 0 2023: 14 2024: 14 2025: 14 2026: 13 2027: 13	2022: 0 2023: 12 2024: 13 2025: 13 2026: 12 2027: 12
Eligible patients*	2022: 223 2023: 4 2024: 3 2025: 3 2026: 3 2027: 3	2022: 146 2023: 2 2024: 2 2025: 2 2026: 2 2027: 2
Treated patients	2022: 200 2023: 204 2024: 207 2025: 210 2026: 213 2027: 216	2022: 131 2023: 133 2024: 135 2025: 137 2026: 139 2027: 141

Source: Table 4.1, p21 of the resubmission

2HCl = dihydrochloride; AEMP = approved ex-manufacturer price; DPA = D-penicillamine; DPMQ = dispensed price per maximum quantity; WD = Wilson disease

***** To avoid double counting, prevalent patients are counted in Year 1 only. The incident population is estimated as the yearly growth in the prevalent pool due to overall growth of the Australian population.

4.14 The estimated net financial impact to the PBS/RPBS for the listing of trientine 2HCl 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 $40 million to < $50 million over the first six years of listing.

Table 7: Estimated utilisation and cost of trientine 2HCl (effective price)

	2022	2023	2024	2025	2026	2027
Patients treated	[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: Tables 4.7, and 4.8 p26 and Table 4.9, p27 of the resubmission
2HCl = dihydrochloride; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
a. Resubmission assumed 7.34 prescriptions per patient per year of treatment
The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000
[3] $0 to < $10 million

4.15 The resubmission performed a number of sensitivity analyses which addressed potential sources of uncertainty in the utilisation of trientine 2HCl, including the prevalence of WD, the proportion of patients who are intolerant to DPA, the proportion of patients with a neurological manifestation of WD, uptake and the daily dose.

4.16 The resubmission proposed a RSA in which use of trientine 2HCl beyond the net cost to the PBS/RPBS presented in Table 7 would be subject to a [redacted]% rebate, which would make the cost of trientine 2HCl equivalent to the cost of DPA. This was based on a cost-minimisation analysis between DPA and trientine 2HCl.

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

5 PBAC Outcome

5.1 The PBAC did not recommend trientine dihydrochloride (2HCl) 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 2HCl, minor changes to the utilisation and financial impact estimates 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 2HCl, 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 2HCl 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 2HCl 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 no active treatment 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 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 the benefit was poorly supported by 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 2HCl was reduced by % 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 2HCl versus no active treatment. The PBAC considered that as the issues from November 2021 remained, the economic evaluation was again uninformative.

5.6 The PBAC noted that the resubmission made some changes to the November 2021 utilisation and financial impact estimates including restricting use to patients aged 6 years and older, reducing the proportion of patients intolerant to DPA from 25% to 17.7% and applying the reduced effective price of trientine 2HCl. The PBAC considered that the financial estimates remained high and uncertain due to uncertainties surrounding the epidemiology of WD and the effective price of trientine 2HCl applied.

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 2HCl differently to other applications. The PBAC noted the % price reduction, revised financial impact estimates 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 2HCl should address the substantially higher drug cost per patient for trientine 2HCl 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 2HCl. The PBAC considered that if the price was reduced as suggested in paragraph 5.9 an 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

6 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.

7 Sponsor's Comment

The sponsor continues to work with PBAC to find a path forward for this product.