

**5.18 TRIENTINE,
Capsule containing trientine dihydrochloride
250 mg (equivalent to 166.7 mg trientine)
Trientine Dr.Reddy's®,
Dr Reddy's Laboratories (Australia) Pty Ltd**

1 Purpose of Submission

- 1.1 The Category 3 submission requested a General Schedule, Authority Required listing for Trientine Dr.Reddy's® brand of trientine dihydrochloride 250 mg capsules (herein referred to as "Dr.Reddy's") for the chelation of elevated copper levels in a patient with Wilson Disease (WD) under the same circumstances as the PBS-listed Trientine Waymade® brand of trientine dihydrochloride 250 mg capsules (herein referred to as "Waymade").

2 Background

- 2.1 Waymade was recommended by the PBAC in May 2022 and is currently listed on the PBS as an Authority Required (Telephone/Online) listing for the chelation of elevated copper levels in WD where penicillamine intolerance exists. Listing was effective from 1 October 2022.

Registration status

- 2.2 Dr.Reddy's was approved by the Therapeutic Goods Administration (TGA) and registered on 29 March 2021 for the treatment of patients with WD who are intolerant of penicillamine.

Previous PBAC consideration

- 2.3 Dr.Reddy's has not been considered by the PBAC previously. The PBAC does not usually consider submissions seeking to list a new brand of an existing pharmaceutical item. In this instance, the applicant did not have a TGA issued bioequivalence statement between the Dr.Reddy's branded product to the existing PBS listed item. Therefore, the Department could not process the submission as a generic brand listing and referred the matter to the PBAC for advice.

3 Requested listing

- 3.1 The submission requested the following changes to the existing listing. A shortened version of the requested listing is presented below. Suggested additions are in italics and deletions are in strikethrough.

Public Summary Document – July 2023 PBAC Meeting

Category / Program: GENERAL - General Schedule (Code GE)						
MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands	
medicinal product pack						
TRIENTINE						
trientine dihydrochloride 250 mg capsule, 100	13124R MP NP	2	200	5	Trientine Waymade Trientine Dr.Reddy's	
<p>Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 am to 5pm EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7004 Special Pricing Arrangements apply.</p>						
<p>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.</p>						
<p>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.</p>						
PBS Indication: Wilson's Disease <i>Chelation of elevated copper levels</i>						
Treatment phase: Initial and continuing <i>[blank]</i>						
<p>Clinical criteria: Patient must have a diagnosis of Wilson disease,</p>						
AND						
<p>Clinical criteria: Patient must be intolerant to penicillamine.</p>						
<p>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 be completed by the specialist prescriber; 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.</p>						

Prescribing Instructions:

Prior to seeking the initial authority approval, 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 grams/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 thrombocytopenia/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.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The submission nominated Waymade as the main comparator as it contains the same active substance (trientine dihydrochloride), is the same strength (250 mg), and is the same form (formulated as a capsule). This was appropriate.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item.

Consumer comments

- 5.2 The PBAC noted and welcomed input from the National Paediatric Medicines Forum via the Consumer Comments facility on the PBS website. The comments highlighted that there have been continuous issues with medicine shortages affecting paediatric patients and welcomed the listing of an additional brand of trientine. The PBAC noted that this advice was supportive of listing Dr.Reddy's.

Clinical trials

- 5.3 The submission presented the following bioequivalence studies between Dr.Reddy's and the Syprine[®] brand of trientine dihydrochloride 250 mg capsules (Syprine) that formed the basis of the TGA's Clinical Evaluation Report and Delegate's Overview.

Syprine is not registered on the ARTG, it is manufactured and available in the US. As a Category 3 submission, the clinical evidence was not independently evaluated.

Table 1: Studies presented in the submission

Trial ID	Protocol/Publication title	Study Objectives	Study Drug and Dose	No. of Subjects/ Patients Assigned to Treatment
Study 15-VIN-747	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Trientine Hydrochloride Capsules USP 250 mg of Dr. Reddy's Laboratories Limited, India comparing with Syprine® (Trientine Hydrochloride) Capsules 250 mg of Valeant Pharmaceuticals International, Inc., USA in healthy, adult, human subjects under fasting conditions.	The objective of this study was to assess the bioequivalence between Trientine Hydrochloride Capsules USP 250 mg of Dr. Reddy's Laboratories Limited, India comparing with Syprine Capsules 250 mg of Valeant Pharmaceuticals International, Inc., USA in normal, healthy, adult, human, subjects under fasting conditions and to monitor adverse events and ensure the safety and tolerability of subjects.	Trientine Hydrochloride Capsules USP 250 mg	58 healthy subjects
Study 17-VIN-0021	An open-label, 2-period, 2-sequence, 2-treatment, crossover, single-dose, fasting bioequivalence study of Waymade-Trientine 250 mg capsules compared to Syprine 250 mg capsules.	Compare the rate and extent of absorption of trientine from the 2 formulations to determine bioequivalence.	Syprine (trientine hydrochloride) 250 mg capsules	44 healthy subjects

Comparative effectiveness and harms

- 5.4 The submission stated that Dr.Reddy's and Waymade share the same primary study as the evidence for efficacy and safety (Weis et al.,2013).
- 5.5 The submission also presented an indirect comparison between Dr.Reddy's and Waymade using the Bucher method of bioequivalent data (Bucher et al., 1997; Gwaza et al., 2012) from Study 15-VIN-747 and Study 17-VIN-0021 to compare its relative efficacy and safety.
- 5.6 The outcomes of the comparison are maximum concentration (C_{max}), area under concentration time curve from time zero to last measurable concentration (AUC_{0-t}) and area under concentration time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$). This was demonstrated through Table 2 and Figure 1.

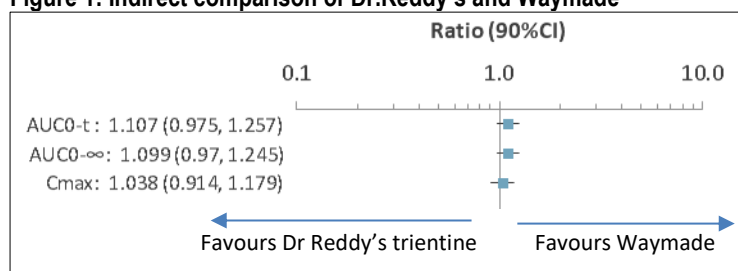
Table 2: Indirect comparison of Dr.Reddy's and Waymade

Outcome	Ratio DrR/Syprine (90% CIs)	Ratio Waymade/Syprine (90% CIs)	Indirect estimate (90% CIs)
AUC _{0-t} (hr*ng/mL)	106.17 (97.76 - 115.31)	95.91 (87.08 - 105.64)	1.107 (0.975, 1.257)
AUC _{0-∞} (hr*ng/mL)	105.37 (97.17 - 114.27)	95.86 (87.21 - 105.38)	1.099 (0.97, 1.245)
C _{max} (ng/mL)	102.65 (93.84 - 112.28)	98.87 (90.34 - 108.21)	1.038 (0.914, 1.179)

Source: TGA Australian Public Assessment Report for Trientine dihydrochloride, p14 Table 4; TGA Delegate's Summary Dr.Reddy's Trientine, pg 7 Table 2.

AUC_{0-t} (hr*ng/mL) = area under concentration time curve from time zero to last measurable concentration; AUC_{0-∞} (hr*ng/mL) = area under concentration time curve from time zero extrapolated to infinity; Cis = confidence intervals; C_{max} (ng/mL) = maximum concentration; DrR = Dr.Reddy's trientine.

Figure 1: Indirect comparison of Dr.Reddy's and Waymade



Source: Submission main body.

AUC_{0-t} (hr*ng/mL) = area under concentration time curve from time zero to last measurable concentration; AUC_{0-∞} (hr*ng/mL) = area under concentration time curve from time zero extrapolated to infinity; Cis = confidence intervals; C_{max} = maximum concentration.

5.7 The submission claimed that there was no statistically significant difference between Dr.Reddy's and Waymade for the outcomes of:

- AUC_{0-t} (Risk Ratio (RR) 1.107, CI: 0.975, 1.257, p=0.1883),
- AUC_{0-∞} (RR 1.099, CI: 0.97, 1.245, p=0.2118), and
- C_{max} (RR 1.038, CI: 0.914, 1.179, p=0.6277).

Clinical claim

5.8 The submission stated that the bioequivalence between Dr.Reddy's and Syprine and between Waymade and Syprine has been determined by the TGA. The bioequivalence between Dr.Reddy's and Waymade has not been determined by the TGA as a direct bioequivalence study between the two products has not been provided to the TGA for evaluation.

5.9 The submission claimed that Dr.Reddy's can be considered therapeutically equivalent to Waymade.

5.10 The PBAC considered the claim of non-inferior comparative effectiveness and non-inferior comparative safety of Dr.Reddy's compared with Waymade was reasonable.

Economic analysis

5.11 The submission did not present an economic analysis. The submission proposed that Dr.Reddy's has the same AEMP as Waymade.

Estimated PBS usage and financial implications

- 5.12 It is expected that Dr.Reddy's would substitute for Waymade within the existing market and therefore the listing is not expected to result in a cost to Government.

6 PBAC Outcome

- 6.1 The PBAC recommended the listing of Dr. Reddy's for the chelation of elevated copper levels in a patient with WD under the same circumstances as Waymade on a cost-minimisation basis.
- 6.2 The PBAC agreed that Waymade is an appropriate comparator.
- 6.3 The PBAC noted that a bioequivalence statement from the TGA was not available for Dr. Reddy's but considered that it was therapeutically equivalent to Waymade. The PBAC considered that the clinical evidence presented adequately demonstrated the non-inferior effectiveness and safety of Dr.Reddy's to Waymade.
- 6.4 The PBAC noted that the submission requested the same AEMP as Waymade and considered that the new listing of Dr. Reddy's should be cost-neutral to Government.
- 6.5 The PBAC advised that, under Section 101(4AACD) of the Act, Dr.Reddy's and Waymade should be marked as equivalent in the Schedule of Pharmaceutical Benefits for the purposes of substitution (i.e. 'a' flagged).
- 6.6 The PBAC advised that, because Dr.Reddy's is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the currently listed Waymade, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 6.7 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new brand as follows:

Public Summary Document – July 2023 PBAC Meeting

Category / Program: GENERAL - General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	<i>(add brand shown in italics)</i> Available brands
TRIENTINE					
trientine dihydrochloride 250 mg capsule, 100	13124R MP NP	2	200	5	^a Trientine Waymade ^a Trientine Dr.Reddy's
Restriction Summary 13321 / Authority Required					
	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.				
	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.				
	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 be completed by the specialist prescriber; 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 approval, 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.				

	<p>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 grams/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 thrombocytopenia/leukopenia, (xiii) lupus-like syndrome (haematuria, proteinuria, positive antinuclear antibody), (xiv) arthralgia.</p>
	<p>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.</p>

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

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.