



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Trientine dihydrochloride

Proprietary Product Name: Trientine-Reddy's /
Trientine-RZ / Trientine Dr.Reddy's /
Trientine-DRLA

Sponsor: Dr. Reddy's Laboratories Australia Pty
Ltd

November 2021

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright

© Commonwealth of Australia 2021

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

List of abbreviations	4
I. Introduction to product submission	5
Submission details _____	5
Product background _____	6
Regulatory status _____	7
Product Information _____	8
II. Registration timeline	8
III. Submission overview and risk/benefit assessment	9
Quality _____	10
Nonclinical _____	10
Clinical _____	11
Risk management plan _____	26
Risk-benefit analysis _____	28
Outcome _____	31
Attachment 1. Product Information	31

List of abbreviations

Abbreviation	Meaning
AAN	Australian Approved Name
ACM	Advisory Committee on Medicines
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AST	Aspartate transaminase
CMI	Consumer Medicines Information
DLP	Data lock point
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk management plan
SAS	Special Access Scheme
UK	United Kingdom
US(A)	United States (of America)
USP	United States Pharmacopeia

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product names:</i>	Trientine-Reddy's, Trientine-RZ, Trientine Dr.Reddy's and Trientine-DRLA
<i>Active ingredient:</i>	Trientine dihydrochloride
<i>Decision:</i>	Approved
<i>Date of decision:</i>	15 February 2021
<i>Date of entry onto ARTG:</i>	29 March 2021
<i>ARTG numbers:</i>	329314, 329315, 329316, 329317
<i>, Black Triangle Scheme:¹</i>	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
<i>Sponsor's name and address:</i>	Dr Reddy's Laboratories (Australia) Pty Ltd Suite 3, Level 3, 390 St Kilda Road Melbourne, VIC, 3004
<i>Dose form:</i>	Capsule
<i>Strength:</i>	250 mg
<i>Container:</i>	Bottle
<i>Pack size:</i>	100
<i>Approved therapeutic use:</i>	<i>Trientine dihydrochloride capsules are indicated for the treatment of patients with Wilson's disease who are intolerant of penicillamine.</i>
<i>Routes of administration:</i>	Oral
<i>Dosage:</i>	The doses are expressed in terms of trientine dihydrochloride and the equivalent dose of trientine free base. Each capsule contains 250 mg of trientine dihydrochloride, equivalent to 167 mg trientine free base. This should be considered if a patient is transferred from one trientine formulation to another.

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

The daily dose of trientine dihydrochloride capsules should be increased only when the clinical response is not adequate or the concentration of free serum copper is persistently above 20 µg/dL (3.1 µmol/L). Optimal long-term maintenance dosages should be determined at 6 to 12 month intervals (see Section 4.4 Special warnings and precautions for use; effects on laboratory tests of the Product Information).

It is important that trientine dihydrochloride capsules be given on an empty stomach, at least one hour before meals or two hours after meals and at least one hour apart from any other drug, food, or milk. The capsules should be swallowed whole with water and should not be opened or chewed.

Children aged 5 years or older

500 to 750 mg trientine dihydrochloride /day (2 or 3 capsules) given in divided doses two or three times daily. This may be increased to a maximum of 1500 mg/day (6 capsules) for children aged 5 years or older. The paediatric dosage in terms of trientine free base is from 333 to 500 mg/day, up to a maximum of 1000 mg/day.

The initial dose for children aged 5 or more years can be expressed on a weight basis as 20 mg trientine dihydrochloride per kilogram of bodyweight in 2 or 3 divided doses, rounded up to the nearest number of whole capsules.

Adults

750 to 1250 mg trientine dihydrochloride /day (3 to 5 capsules) given in divided doses two, three or four times daily. This may be increased to a maximum of 2000 mg/day for adults. The adult dosage in terms of trientine free base is from 500 to 833 mg/day up to a maximum of 1333 mg/day.

Pregnancy category:

D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Dr Reddy's Laboratories Australia Pty Ltd (the sponsor) to register Trientine Dr.Reddy's, Trientine-Reddy's, Trientine-RZ, and Trientine-DRLA (trientine dihydrochloride) 250 mg capsules for the following proposed indication:

Trientine dihydrochloride capsules are indicated in the treatment of patients with Wilson's disease in adults, adolescents and children > 5 years who are intolerant of penicillamine.

Wilson's disease, also known as hepatolenticular degeneration, is an inherited autosomal recessive disorder in which defective cellular copper transportation leads to reduced biliary excretion of copper and accumulation of copper in tissues, initially in the liver, but also in the brain, kidneys and cornea (the latter classically characterised by the appearance Kayser-Fleischer rings, or dark rings that appear to encircle the iris, as a result of copper deposition). Wilson's disease is caused by mutations of the *ATP7B* gene on chromosome 13, which encodes a copper-transporting ATPase (Wilson disease protein, also known as ATP7B) in the liver. The condition affects about 1 in 30,000 people and most commonly presents between the ages of 5 and 35 years, although it may be diagnosed at any age.

Wilson's disease requires lifelong treatment to remove excess copper deposits in the tissues and to prevent reaccumulation. Chelating agents, including D-penicillamine (penicillamine) and trientine, have been used for many years to remove excess copper. Penicillamine has been used for the treatment of Wilson's disease since 1956, and has been included on the Australian Register of Therapeutic Goods since 1994. Penicillamine has generally been used as the primary chelating agent, but its long-term use can be limited by adverse effects in about 30% of patients. Trientine was first registered in the United States of America (USA) and United Kingdom (UK) in 1985, but has been in clinical use since 1969 as an alternative to penicillamine. There are no controlled trials comparing these chelating agents, so their use is based mainly on observational data and clinical experience. Other treatment options for Wilson's disease include zinc and tetrathiomolybdate.

Regulatory status

At the time the TGA accepted this submission and evaluation of this submission commenced trientine dihydrochloride had not been approved by the TGA, and no products containing trientine dihydrochloride had been registered on the Australian Register of Therapeutic Goods (ARTG).

Despite never having been registered on the ARTG, historically, the supply of 250 mg formulations of trientine to patients with Wilson's disease has been facilitated through the Special Access Scheme (SAS) for many years.²

On 9 October 2019, the TGA approved an application by the sponsor for orphan designation and designated trientine dihydrochloride as an orphan drug for the treatment of Wilson's disease on 9 October 2019.³

² The **Special Access Scheme (SAS)** allows certain health practitioners to access therapeutic goods (such as medicines, medical devices or biologicals) that are not included in the Australian Register of Therapeutic Goods (ARTG) for a single patient. Therapeutic goods that are not included in the ARTG (and are not otherwise exempt from being in the ARTG) are described by us as 'unapproved'.

³ **Orphan drugs** are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

During the evaluation of this submission, a similar literature based submission for trientine dihydrochloride, with the product name Trientine Waymade, and was registered on the ARTG in January 2021.⁴

Overseas regulatory status

United States of America

Syprine (trientine hydrochloride 250 mg capsules);⁵ was registered in the USA on 8 November 1985. Dr Reddy's Trientine Hydrochloride Capsules USP 250 mg were registered in the USA on 7 March 2019 as a generic of Syprine. A bioequivalence study was used to support registration is presented in the Australian dossier. The US indication is:

Trientine hydrochloride capsules are indicated in the treatment of patients with Wilson's disease who are intolerant of penicillamine. Clinical experience with trientine hydrochloride is limited and alternate dosing regimens have not been well-characterized; all endpoints in determining an individual patient's dose have not been well defined. Trientine hydrochloride and penicillamine cannot be considered interchangeable. Trientine hydrochloride capsules should be used when continued treatment with penicillamine is no longer possible because of intolerable or life endangering side effects.

Unlike penicillamine, trientine hydrochloride capsules are not recommended in cystinuria or rheumatoid arthritis. The absence of a sulfhydryl moiety renders it incapable of binding cysteine and, therefore, it is of no use in cystinuria. In 15 patients with rheumatoid arthritis, trientine hydrochloride was reported not to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment.

Trientine hydrochloride capsules are not indicated for treatment of biliary cirrhosis.

At the time of this submission, Dr Reddy's Trientine Hydrochloride Capsules USP 250 mg are not registered in any other country/region.

European Union and United Kingdom

Other trientine products have marketing authorisation in Europe and the UK, including trientine dihydrochloride 300 mg capsules by Univar Solutions BV which have been registered in the UK since 1985, and trientine dihydrochloride 300 mg capsules (product name, Cufence) which were registered in Europe in 2019.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

⁴ AusPAR Trientine Waymade trientine dihydrochloride Waymade Australia Pty Ltd PM-2019-05976-1-3 <https://www.tga.gov.au/auspar/auspar-trientine-dihydrochloride>

⁵ This is a dihydrochloride formulation, referred to in USA as hydrochloride.

Table 1: Timeline for Submission PM-2020-00155-1-3

Description	Date
Designation (Orphan); ³	9 October 2019
Submission dossier accepted and first round evaluation commenced	31 March 2020
First round evaluation completed	2 September 2020
Sponsor provides responses on questions raised in first round evaluation	24 November 2020
Second round evaluation completed	15 December 2020
Delegate's Overall benefit-risk assessment	14 January 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	15 February 2021
Completion of administrative activities and registration on the ARTG	29 March 2021
Number of working days from submission dossier acceptance to registration decision*	160

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The following guidance documents were considered applicable to this submission:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr., 16 June 2011.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Trials in Small Populations. European Medicines Agency; CHMP/EWP/83561/2005, 27 July 2006.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 9 November 2016.
- Therapeutic Good Administration (TGA) Literature based submissions, 27 May 2014.⁶

⁶ Therapeutic Good Administration (TGA) Literature based submissions, 27 May 2014. Available at: <https://www.tga.gov.au/publication/literature-based-submissions>.

Quality

The strength of this product is expressed as the dihydrochloride salt (250 mg) rather than the free base (167 mg). This is consistent with Dr Reddy's Trientine Hydrochloride Capsules USP 250 mg, registered in USA in 2019 as a generic of Syprine. Syprine has been registered in USA since 1985 and its strength is expressed as the hydrochloride salt (250 mg). Based on the history of this product internationally, the proposed labelling is considered acceptable.

There are no outstanding issues with the quality evaluation. The Product Information (PI) is acceptable from a quality perspective. The quality evaluator has no objection to the registration of the proposed products.

Nonclinical

The nonclinical dossier was based on published literature.

The oral bioavailability of trientine was low, and was negatively affected by food in rats. Distribution of trientine was observed to the liver and kidney. Trientine only minimally crossed the blood-brain barrier. Both SSAT2 and SSAT1 were found to acetylate trientine. Urinary excretion was the main route of excretion for absorbed trientine-related material in rats. The set of *in vitro* pharmacokinetic drug interaction studies was limited, but this should not preclude registration.

Primary pharmacology studies showed copper chelation activity in all animal species tested, supporting the use of this medicine for the proposed indication. No preclinical studies in juvenile animals were submitted, so support for use in paediatric patients is reliant on clinical data. Lower efficacy in reducing brain levels of copper was seen in animals, consistent with the poor ability of the drug to cross the blood-brain barrier. The monoacetylated metabolite, monoacetyltrientine, may contribute to the efficacy of trientine.

Repeat-dose toxicity studies in mice, rats and dogs showed histopathological changes in the lungs (interstitial inflammation and broncho-alveolar pneumonia) in all species. These pulmonary effects were assessed as likely due to the pharmacological action of trientine. This has been added to the Nonclinical safety specification in the risk management plan.

Trientine was genotoxic in some *in vitro* studies, but negative in an adequately conducted mammalian gene mutation assay and consistently negative in *in vivo* mouse micronucleus studies. There was no carcinogenicity study for orally administered trientine. The absence of a carcinogenicity study for oral trientine is acceptable based on negative results in *in vivo* genotoxicity studies, negative findings of tumours or other proliferative lesions at the application site in a mouse dermal carcinogenicity study, the absence of concerning findings in the repeat-dose studies, and the long history of clinical use.

The set of reproductive and development studies was limited, but this should not preclude registration. Embryofetal development studies suggest some teratogenic potential of trientine. The evaluator recommends Pregnancy Category D.⁷

The draft PI is acceptable from the nonclinical perspective.

⁷ **Pregnancy Category D:** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Clinical

This is a literature-based submission involving a systematic literature search strategy approved by the TGA. The use of a literature-based submission to support the registration of a new chemical entity was accepted based on the long history of market authorisation of trientine internationally.

The clinical dossier consisted 42 study reports and research publications included as clinical study reports, and a further 9 references, which included clinical guidance documents for the treatment of Wilson's disease and the European Medicine Agency's ePAR (European Public Access Report) for one trientine product.

Eight published studies and one overview report that provided pharmacokinetic and pharmacodynamic outcomes:

- four studies that characterised the pharmacokinetics after a single oral dose of trientine in healthy volunteers, including one bioequivalence study;
- one study that described the pharmacokinetics of trientine after multiple doses of trientine in healthy volunteers;
- two studies that described the pharmacokinetics and/or pharmacodynamics of trientine in patients with Wilson's disease;
- one pharmacokinetic/pharmacodynamic modelling study in healthy volunteers; and
- one overview.

Ten published efficacy studies, three reviews and four abstracts for conference presentations were submitted to support claims for efficacy.

Fifteen additional published reports, including individual case studies, were included to support claims for safety.

Three clinical practice guidelines published by the relevant European and US specialist associations, which were included among additional literature references, were considered.

In addition, the sponsor included a clinical overview and a clinical summary, which in turn included summaries of clinical pharmacology, clinical efficacy, and clinical safety that provided synopses of the reports included in the literature based submission.

Pharmacology

The published literature describing the pharmacology of trientine is detailed in the clinical evaluation report. A summary of the main pharmacokinetic and pharmacodynamic findings is provided below.

Pharmacokinetics

Bioequivalence of the proposed product to the USA reference product, Syprine, was established in Study 15-VIN-474.

Table 2: Study 15-VIN-474 Bioequivalence of Dr Reddy's trientine hydrochloride capsules USP 250 mg (test) versus Syprine 250 mg capsules (reference)

For Trientine:		
Parameters (Units)	Arithmetic Mean \pm SD (%CV) (N = 55)	
	Reference Product (R)	Test Product (T)
C_{max} (ng/mL)	558.470 \pm 219.4803 (39.30%)	575.715 \pm 237.7750 (41.30%)
T_{max} (hr)	1.250 (0.33- 4.00)	1.250 (0.50 - 3.00)
AUC _{0-t} (hr*ng/mL)	2273.043 \pm 1038.0556 (45.67%)	2394.601 \pm 1046.6259 (43.71%)
AUC _{0-∞} (hr*ng/mL)	2393.740 \pm 1065.3854 (44.51%)	2506.882 \pm 1084.2177 (43.25%)
$t_{1/2}$ (hr)	10.216 \pm 6.0591 (59.31%)	9.572 \pm 4.9196 (51.39%)
K_{el} (1/hr)	0.096 \pm 0.0594	0.096 \pm 0.0542

%CV = coefficient of variation; AUC_{0-t} = area under the concentration versus time curve from time zero to last quantifiable measurement; AUC_{0-∞} = area under the concentration versus time curve from time zero to infinity; C_{max} = maximum concentration; K_{el} = elimination constant; N = number of subjects; $t_{1/2}$ = half life; SD = standard deviation; T_{max} = time of maximum concentration.

Table 3: Study 15-VIN-474 Statistical analysis, bioequivalence of Dr Reddy's trientine hydrochloride capsules USP 250 mg (test) versus Syprine 250 mg capsules (reference)

Trientine Hydrochloride capsule USP 250 mg (No of subjects completed=55) Dose (250 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No.: 15-VIN-474)						
Parameter	Test	N	Reference	N	Ratio	90% C.I.
AUC _{0-t} (hr*ng/mL)	2185.601	55	2058.528	55	106.17	97.76 % - 115.31%
AUC _{0-∞} (hr*ng /mL)	2293.342	55	2176.426	55	105.37	97.17 % - 114.27%
C_{max} (ng/mL)	530.529	55	516.840	55	102.65	93.84 % - 112.28%

AUC_{0-t} = area under the concentration versus time curve from time zero to last quantifiable measurement; AUC_{0-∞} = area under the concentration versus time curve from time zero to infinity; C.I. = confidence intervals; C_{max} = maximum concentration; N = number of subjects.

Absolute bioavailability was not reported in the literature. Following oral administration, absorption of trientine is low and variable. The pharmacokinetics of trientine is similar between healthy individuals and patients with Wilson's disease. Trientine displays linear pharmacokinetics. There is high inter-individual variability in the pharmacokinetics of trientine.

Pharmacokinetic studies in the healthy population were predominantly performed under fasting conditions. The literature lacked robust data on the effect of food on the pharmacokinetics of trientine, but some studies commented that co-administration with food may result in binding with trace metals in the diet and reduced bioavailability of trientine. Trientine is recommended to be taken at least one hour before meals or two hours after meals to allow for maximal absorption and reduce the likelihood of binding with trace metals in the diet.

Trientine is rapidly metabolised to monoacetyltrientine and diacetyltrientine. The extent of the contribution of monoacetyltrientine and diacetyltrientine to the overall effect of

trientine on copper levels is uncertain. Trientine and its metabolites are excreted in the urine. Unabsorbed trientine is eliminated through faecal excretion.

No data on pharmacokinetic interactions were presented.

Pharmacodynamics

The primary pharmacodynamics effect of trientine is to increase renal excretion of copper as the stable trientine-copper complex. Some studies reported decreased absorption of ingested copper with trientine.

There is intra- and inter-individual variability in responsiveness to trientine, but the relationship between trientine dose and urinary copper excretion is generally linear. The cupruritic response to trientine is affected by the degree of copper overload, with smaller responses seen in patients whose copper overload has been controlled.

Dosage

The proposed dosage is based on the US Food and Drug Administration-approved dosage for Syprine.

There were no formal dose finding studies in the literature. The dosages reported in the studies ranged from 100 mg twice daily to 1800 mg twice daily. Cho et al., (2009);⁸ evaluated the pharmacokinetics, pharmacodynamics, tolerability and safety of trientine after repeated twice daily doses of 200, 600, 1200 and 1800 mg for 14 days in adults. The authors concluded that the steady state doses were safe and well tolerated, but the pharmacokinetic/pharmacodynamic and safety profile support a 600 mg twice daily regimen (1200 mg/day) as more adverse events were reported with the higher 3600 mg/day dose.

Trientine has been in clinical use for many years. There is high inter-individual variability in the pharmacokinetics of trientine, and the dose is typically titrated according to clinical response. The Australian Therapeutic Guidelines (December 2019);⁹ list trientine as a treatment for Wilson's disease but do not make specific dose recommendations.

The American Association for the Study of Liver Diseases (AASLD) 2008 practice guidelines advise the following:¹⁰

Typical dosages are 750-1500 mg/day in two or three divided doses, with 750 or 1000 mg used for maintenance therapy. In children, the weight-based dose is not established, but the dose generally used is 20 mg/kg/day rounded off to the nearest 250 mg, given in two or three divided doses. Trientine should be administered 1 hour before or 2 hours after meals.

The European Association for the Study of the Liver (EASL) 2012 Clinical Practice Guidelines for Wilson's Disease advise:¹¹

Typical dosages of trientine are 900-2700 mg/day in two or three divided doses, with 900-1500mg/day used for maintenance therapy. In children, the weight-based dose is not established, but the dose generally used is 20 mg/kg/day rounded off to the nearest 250 mg, given in two or three divided doses'.

⁸ Cho, H. Y. et al. Pharmacokinetic and pharmacodynamic modeling of a copper-selective chelator (TETA) in healthy adults, *J Clin Pharmacol.* 2009; 49(8): 916-928.

⁹ eTG complete. Melbourne: Therapeutic Guidelines Ltd; 2019. Wilson disease

¹⁰ Roberts, E. A. and Schilsky, M.L. American Association for the Study of Liver Diseases (AASLD) Practice guidelines. Diagnosis and treatment of Wilson disease: an update. A practice guideline on Wilson disease, *Hepatology*, 2008; 47(6): 2089-2111.

¹¹ European Association for the Study of the Liver (EASL), Clinical Practice Guidelines: Wilson's disease, *J Hepatology*, 2012; 56: 671-685.

The submission included a summary of 65 Special Access Scheme permits issued between July 2017 and June 2018 for the supply of trientine dihydrochloride to patients in Australia.² The SAS listings did not identify paediatric and adult patients. The total daily dose ranged from 500 mg to 2000 mg, with approximately 50% of patients receiving between 500 to 1250 mg per day, in two or three divided doses. Eleven patients received doses of 1500 mg to 2000 mg per day.

Efficacy

Literature supporting efficacy were presented according to hierarchy of evidence (see Table 4, below). The Levels I and II literature provided very limited data relating to the proposed use of trientine in patients intolerant to penicillamine. The retrospective and prospective studies provide lower level evidence relevant to the proposed indication.

Table 4: Hierarchy of clinical evidence for citations identified in literature searches

Level	Study/type of evidence	Citations
I	Systematic randomised control trial review, meta-analyses	Appenzdeller-Herzog et al., (2019) Wiggelinkhuizen et al., (2009) Brewer et al., (2009)
II	Individual properly designed randomised control trial	Brewer et al, 2006 (n = 48)
III-1	Non-randomised control trial; prospective	Askari (2003); Ala et al., (2015); Weiss et al., (2016a); Weiss et al., (2019)
III-2	Cohort or case-control analytic studies; retrospective studies	Weiss et al., (2013); Weiss et al., (2011); Weiss et al., (2016b); Weiss et al., (2018); Wang et al., (2010); Manolaki et al., (2009) Taylor et al., (2009); Merle et al., (2007); Arnon et al., (2007); Dahlman et al., (1995)
III-3	Case reports / series (safety)	Sabolek et al., (2004); Chung et al., (2016); Boga et al., (2015); Kim et al., (2013); Harada et al., (2011); Perry et al., (1996); Du Bois et al, (1990)

The key studies for this submission are summarised in the following subsections.

*Weiss et al. (2013)*¹²

This was a retrospective cohort study of 380 patients with Wilson's disease treated at six tertiary care centres in Germany and Austria, and 25 patients from the EuroWilson registry.¹³ The purpose of the study was to evaluate the efficacy and safety of

¹² Weiss, K. H. et al. Efficacy and Safety of oral Chelators in Treatment of Patients with Wilson Disease, *Clin Gastroenterol Hepatol*, 2013; 11: 1028-1035.

¹³ EuroWilson was initially funded through the EU Framework Programme 6 from 2004-2008. The overall aim of EuroWilson was to assess the feasibility of mounting randomised controlled trials of treatment in Wilson's disease. This was achieved by establishing a clinical database of newly presenting cases of Wilson's disease and gathering data on the incidence of Wilson's disease, and the numbers of patients within clinically homogenous groups.

trientine and penicillamine therapy, in terms of hepatic and neurological outcomes and adverse events leading to discontinuation.

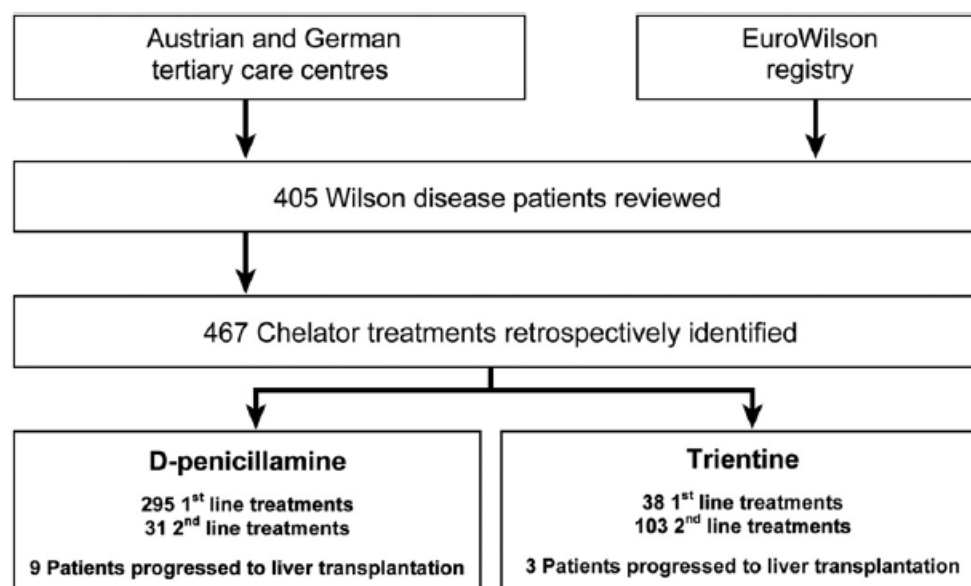
Medical records of the 405 patients were reviewed. Data were collected for a mean of 13.3 years after therapy began. Patients were categorised according to symptoms present at diagnosis: asymptomatic, hepatic, neurologic, or hepatic and neurologic. 207 (51.1%) patients presented with hepatic symptoms only, 92 (22.7%) presented with neurologic symptoms only, 52 (12.8%) presented with hepatic and neurologic symptoms, and 54 (13.3%) were asymptomatic at diagnosis. 21 patients (5.2%) presented with fulminant Wilson's disease with hepatic failure at diagnosis.

Patients with a stable course were assessed in the tertiary centres approximately once a year. Patients were reviewed more frequently (3, 6, and 12 months) after initiating or changing therapy. No systematic criteria were applied in the initial choice of chelating agent.

Hepatic and neurologic outcomes were assessed from patient records at 6, 12, 24, 36 and 48 months after initiation of the treatment. Hepatic outcome measures were based on clinical symptoms, course of liver enzymes, and liver function tests. Neurologic outcomes were evaluated by the physician. Hepatic and neurologic outcomes were scored as unchanged, improved to normal, improved but not normal, deteriorated, or asymptomatic over duration.

The analysis identified 467 chelator-based treatments with a duration of more than 6 months: 326 involved penicillamine monotherapy (295 as first-line, 31 as second-line) and 141 involved trientine monotherapy (38 as first-line and 103 as second-line). No specific dosage information was presented. Zinc treatments were not analysed, and patients who received only zinc salts over the whole treatment period were excluded from the analysis.

Figure 1: Weiss et al. (2013) study overview



EuroWilson's initial purpose is achieved and has established a rich data resource. This is giving data about epidemiology, quality, and current choice of treatments. Follow-up of this uniquely well-documented cohort will give information about outcomes from different treatment regimes, late neurological deterioration, neurological outcome after transplantation, and other current long-term concerns.

Baseline characteristics, recorded at the time of initiation of, or change in, chelator-based treatment, were generally similar across the treatment groups, but penicillamine was used more commonly as first-line treatment.

Hepatic and neurologic improvement and worsening were reported for penicillamine and trientine, stratified by first-line and second-line use (see Table 5).

For trientine in the second-line setting (proposed for registration):

- 31 of 45 (68.9%) patients with hepatic symptoms showed hepatic improvement.
- 10 (22.2%) patients with hepatic symptoms showed stable hepatic disease.
- 4 (8.9%) patients with hepatic symptoms showed hepatic worsening.
- No hepatic worsening was observed in asymptomatic patients.
- 26 of 51 (50.9%) patients with neurologic symptoms showed neurologic improvement.
- 17 (33.3%) patients with neurologic symptoms showed stable neurologic disease.
- 8 (15.7%) patients with neurologic symptoms showed neurologic worsening.
- No neurologic worsening was observed in asymptomatic patients.

Hepatic improvement was lower in the second-line setting compared to the first-line setting for both penicillamine and trientine. The authors attributed this finding to advanced liver disease and irreversible structural liver damage.

Neurologic deterioration occurred more frequently with trientine than penicillamine in both the first-line and second-line settings.

Table 5: Weiss et al. (2013) Rate of hepatic or neurological improvement and worsening in all or only symptomatic patients stratified by first and second-line treatment

	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%)	.859	12/31 (38.7%)	31/103 (30.1%)	.386
Symptomatic	185/204 (90.7%)	25/27 (92.6%)	1	12/16 (75%)	31/45 (68.9%)	.757
Hepatic worsening						
All	4/295 (1.4%)	0/38	1	0/31	4/103 (3.9%)	.573
Symptomatic	4/204 (2%)	0/27	1	0/16	4/45 (8.9%)	.565
Neurologic improvement						
All	77/295 (26.1%)	11/38 (28.9%)	.699	3/31 (9.7%)	26/103 (25.2%)	.082
Symptomatic	77/114 (67.5%)	11/20 (55%)	.312	3/13 (23.1%)	26/51 (51%)	.118
Neurologic worsening						
All	6/295 (2%)	4/38 (10.5%)	.018	1/31 (3.4%)	8/103 (7.8%)	.684
Symptomatic	6/114 (5.3%)	4/20 (20%)	.042	1/13 (7.3%)	8/51 (15.7%)	.672

DPA = D-penicillamine.

Note: P-values were established using the 2-tailed Fisher test.

Walshe et al. (1982)¹⁴

This was a retrospective review of file notes for 20 penicillamine-intolerant patients treated with trientine dihydrochloride for a minimum of one year over the preceding

¹⁴ Walshe, J. M. Treatment of Wilson's Disease with Trientine (Triethylene Tetramine) Dihydrochloride, *Lancet*, 1982; 1(8273): 643-647.

13 years. The aim was to describe the clinical response to trientine in patients with Wilson's disease intolerant to penicillamine. The study reported trientine doses between 400 mg three times daily and 800 mg three times daily before meals.

The analysis grouped patients according to the stage at which they developed penicillamine intolerance: patients in whom penicillamine intolerance developed within days or weeks of commencing treatment (Group A, n = 8); patients who had received less than one year of continuous penicillamine before developing intolerance (Group B, n = 3); and patients who had responded well to penicillamine before developing intolerance at a later stage (Group C, n = 9).

Clinical responses for patients in Group A are shown in Table 6. All patients in Group A experienced improvement in symptoms after treatment with trientine (duration of treatment ranging from 14 to 120 months). The three patients in Group B were reported to have considerable neurological deficit which improved after commencing trientine, although two had some residual deficit. The patients in Group C had been adequately 'de-coppered' at the time of changeover. They remained symptomatically well controlled after changing to trientine, the penicillamine-related toxicities resolved, and no new toxicities were observed other than iron deficiency.

Table 6: Walshe et al. (1982) Clinical and pharmacodynamic response to treatment with trientine after early intolerance to penicillamine (Group A)

Patient	Age at onset (yr)	Age at diagnosis (yr)	Sex	KF rings (density)	Symptoms at presentation (severity)	Time on trien (mo)	KF rings (density)	Symptoms after trien	Caeruloplasmin (mg/dl)	
									Before	After
1	13	15	M	4+	Dysarthria; drooling; tremor; ataxia* (4+)	60	±	Dysarthria only	0	0
2	29	30	F	3+	Dysarthria; titubation; tremor; ataxia; micrographia (3+)	40	±	None	5.3	0
3	..	27	F	+	Hepatomegaly; liver Ca 220µg/g wet weight (0)	14	±	None	1.0	1.3
4	15	15	F	3+	Haemolytic crises; jaundice; nausea + vomiting; oedema; ascites (3+)	24	±	None	14.0	1.5
5	20	22	F	2+	Severe titubation; tremor; ataxia; mild dysarthria; drooling (4+)	44	0	None; two successful pregnancies	1.5	7.1†
6	13	13	M	3+	Sunflower cataracts; mild Parkinsonism; drooling (+)	21	±	None	3.1	0
7‡	..	17	M	+	Mild intention tremor; early cogwheel rigidity (0)	120	±	None	1.2	0
8	..	16	M	+	Slight intention tremor; abnormal liver tests (0)	33	±	None	4.7	1.0

KF rings = Kayser-Fleischer (pericorneal pigment) rings

Scheinberg et al. (1987)¹⁵

Scheinberg and colleagues retrospectively compared the clinical outcomes of three groups of patients with Wilson's disease in the USA. Group 1 comprised 11 patients who had been treated with penicillamine (1000 to 2000 mg/day) for three to 16 years before ceasing treatment (see Table 7). Ten patients in Group 1 were asymptomatic on penicillamine before ceasing treatment. Eight patients died with hepatic failure within six years of ceasing treatment with penicillamine, one required liver transplantation, and two recovered partly or fully with recommencing treatment.

¹⁵ Scheinberg, I. H. et al. The Use of Trientine in Preventing the Effects of Interrupting Penicillamine Therapy in Wilson's Disease, *N Engl J Med*, 1987; 317: 209-213.

Table 7: Scheinberg et al. (1987) Clinical course in patients who ceased treatment with penicillamine, no further treatment

SEX	AGE AT ONSET	CERULO-PLASMIN	HEPATIC COPPER	KAYSER-FLEISCHER RINGS	PENICILLAMINE TREATMENT		FINAL OUTCOME
					WITH	WITHOUT	
	yr	mg/dl*	µg/g of dry weight†		no. of yr		
F	22	13		4+	19	1	Hepatic death
M	14	<20		4+	4	3	Hepatic death
M	(Asymptomatic)	1	956	1+	10	6	Fulminant hepatic death
F	8	2	1717	3+	9	0.75	Fulminant hepatic death
M	32	1	1088	4+	13	1	Fulminant hepatic death
F	(Asymptomatic)	4	768	0	13	3	Fulminant hepatic death
F	(Asymptomatic)	16	385	0	3	4	Fulminant hepatic death
F	(Asymptomatic)	3	777	0	5	2	Fulminant hepatic death
M	(Asymptomatic)	1		4+	12	1	Neurologic disability
*F	6	9		3+	11	0.25	Recovered from hepatic dysfunction
F	11	3	892	3+	16	1	Liver transplantation

* Normal levels are 20 to 50 mg per decilitre.

† Normal levels are < 50 µg/g dry weight.

Group 2 comprised 13 patients who had been treated with penicillamine for 0.5 to 15 years before developing adverse reactions and switching to trientine dihydrochloride (1000 mg to 1500 mg/day) for ongoing therapy (see Table 8). All patients were alive at the time of publication (duration of trientine treatment ranged from 2 to 15 years) except for one patient who died by unrelated accident. Seven were asymptomatic, four were reported to have 'minor neurologic symptoms' and one had psychiatric symptoms. Eight patients recovered fully from penicillamine-related adverse events, four improved, and one patient had no change in the reported adverse event (elastosis perforans serpiginosa) after commencing trientine.

Table 8: Scheinberg et al. (1987) Clinical course in patients intolerant to penicillamine, switched to trientine

SEX	AGE AT ONSET	CERULO-PLASMIN	HEPATIC COPPER	KAYSER-FLEISCHER RINGS	PENICILLAMINE TREATMENT		TRIENTINE TREATMENT		CURRENT SYMPTOMS
					DURATION	REACTION	DURATION	REACTION	
	yr	mg/dl	µg/g of dry weight		yr		yr		
F	16	7.8		3+	9	Pemphigus	8	Disappeared	None
M	14	1		3+	1	Nephrosis	15	Disappeared	None
M	18	<20		3+	1	Nephrosis	2	Disappeared	(Accidental death)
F	21	4.3		4+	1	Thrombocytopenia	9	Improved	Minor neurologic symptoms
M	19	<20		4+	7	Nephrosis	14	Disappeared	Minor neurologic symptoms
F	16	12		4+	1	Nephrosis	6	Disappeared	None
F	(Asymptomatic)	10	349	0	15	Elastosis	2	Unchanged	None
M	47	15		4+	7	Nephrosis	5	Improved	Psychiatric symptoms
F	(Asymptomatic)	<20		4+	5	Lupus	4	Disappeared	None
F	16	14		4+	0.5	Thrombocytopenia	3	Improved	None
M	17	<20		4+	1	Neutropenia	4	Improved	Minor neurologic symptoms
F	(Asymptomatic)	<20	402	2+	1	Nephrosis	4	Disappeared	None
F	44	8		4+	1	Thrombocytopenia	4	Disappeared	Minor neurologic symptoms

A third group of 320 patients remained on treatment with penicillamine. Outcomes in this group are not directly relevant to the proposed indication.

Brewer et al. (2006)¹⁶

This was a USA-based randomised, double-blind, controlled study comparing trientine and tetrathiomolybdate in the treatment of primarily newly diagnosed patients with Wilson's disease with neurologic symptoms.

23 patients received trientine hydrochloride 500mg twice daily and 25 patients received tetrathiomolybdate 20 mg six times daily for eight weeks. All patients also received zinc co-therapy. Patients were monitored in hospital for eight weeks, with neurologic and speech functions assessed weekly. After eight weeks, they were discharged home on zinc 50 mg three times daily and were reviewed annually for three years.

The trientine group (11 males, 12 females) were aged between 13 and 43 years (seven were aged 18 or younger). Seven had previously been treated with penicillamine (no more than 28 days) and two had previously been treated with trientine (7 days and 21 days respectively).

Six of 23 (26%) patients in the trientine arm and 1 of 25 (4%) patients in the tetrathiomolybdate arm underwent neurologic deterioration ($p < 0.05$). Speech recovery was fair and did not differ between the 2 arms. The authors concluded that tetrathiomolybdate is a better choice than trientine for preserving neurologic function in patients who present with neurologic disease.

Dahlman et al. (1995)¹⁷

This was a case series of 19 patients with Wilson's disease, 17 of whom were treated initially with penicillamine and subsequently switched to trientine due to adverse effects, lack of improvement or worsening of neurological symptoms, and two of whom were treated with trientine from diagnosis. Trientine doses ranged from 1000 mg to 1800 mg per day, and duration of treatment ranged from 4 months to 17.5 years. Efficacy was evaluated based on clinical symptoms and Kayser-Fleischer rings (see Table 9). The authors reported that all patients responded well to trientine with the exception of one patient who was treated initially with trientine and developed neurological deterioration. 13 remained on trientine at final review, and the mean duration of trientine treatment was 8.5 years.

¹⁶ Brewer, G. J. et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease, *Arch Neurol*, 2006; 63(4): 521-527.

¹⁷ Dahlman, T. et al. Long-term Treatment of Wilson's Disease with Triethylene Tetramine Dihydrochloride (Trientine), *QJ Med*, 1995; 88: 609-616.

Table 9: Dahlman et al. (1995) Change in Wilson's disease signs and symptoms with trientine

At the time of diagnosis		Present status	
KF	Other symptoms	KF	Other symptoms
+	Haemolytic crisis, jaundice, ascites, cholelithiasis, proteinuria	-	No symptoms
++	Dysarthria, ataxia	-	Severe dystonia, muscle contractures
+	Tremor, chorea	(+)	No symptoms
+	Dysarthria, tremor, ataxia	-	Dead; adenocarcinoma involving liver
++	Dysphagia, dysarthria, tremor, personality changes	(+)	Mild dysarthria
+	Abnormal liver tests, haemolysis	-	No symptoms
+	Epilepsia, haemolysis, thrombocytopenia	+	Impaired liver function, thrombocytopenia
+	Dysphagia, tremor, ataxia	-	No symptoms
+	Abnormal liver tests, dysarthria, ataxia, glucosuria	-	Moderate dysarthria, mild dystonia
+	Jaundice, K-F rings observed on optician examination	-	Dead; adenocarcinoma involving liver
+	Haemolytic anemia, icterus, splenomegaly, haematuria	-	Dead; splenic rupture
+	Abnormal liver tests	-	No symptoms
+	Dysarthria, dysphagia, gait disturbances	+	Mild dysarthria
+	Oedema, ascites, thrombocytopenia, personality changes	-	No symptoms, liver transplanted
+	Tremor, dysarthria, concentration difficulties	(+)	No symptoms
*	Dysarthria, writing problems, gait disturbances	-	Mild dysarthria, slight atethosis
*	Ascites	-	No symptoms, liver transplanted
(+)	Jaundice, ascites, tremor, dysarthria	-	No symptoms
+	Dysarthria, dysphagia, tremor	-	Mild dysarthria, mild dystonia, EPS

EPS = elastosis perforans serpiginosa; KF = Kayser-Fleischer rings.

Symptoms referred to as mild or moderate in 'Present status' were more severe at the time of diagnosis.

* No data available.

Kayser-Fleischer ring status: - = absent; (+) = narrow; + = moderate; ++ = wide.

Arnon et al. (2007)¹⁸

This was a retrospective review of the clinical records of children with Wilson's disease treated in the paediatric liver/liver transplant unit of the Mount Sinai Medical Center (New York, USA) between 1998 and 2006. The objective was to evaluate the efficacy of, and adherence to, trientine therapy (250 to 500 mg twice daily, around 20 mg/kg/day) and/or zinc therapy (25 to 50 mg twice daily, around 1 to 2 mg/kg/day). This study assessed trientine as first-line therapy, not following intolerance to penicillamine. Zinc was added once adequate chelation had been achieved. Efficacy was assessed by measuring serum alanine transaminase (ALT) and aspartate transaminase (AST), and 24 hour urine copper.

Of the 22 patients, 7 presented with acute liver failure requiring liver transplantation at admission, and 15 commenced trientine. Mean ALT levels decreased from 183 IU at presentation (n = 10) to 80 IU at 12 months (n = 10) and 66 IU at 18 months (n = 7). Mean 24-hour urinary copper levels increased from 156 µg at presentation to 494 µg at one to 2 months, then decreased to 72 µg after 12 months of treatment.

¹⁸ Arnon, R. et al. Wilson Disease in Children: Serum Aminotransferases and Urinary Copper on Triethylene Tetramine Dihydrochloride (Trientine) Treatment, *J Ped Gastroent Nutr*, 2007; 44: 596-602.

Weiss et al. (2018); Weiss et al. (2019)^{19,20}

The submission included published conference extracts (Weiss 2018, Weiss 2019) relating to Study UNV-TRI-002. This study, which comprised a retrospective study followed by a prospective study, supported the European Medicines Agency's (EMA) marketing authorisation of Cufence (trientine dihydrochloride) by Univar Solutions BV in Europe on 25 July 2019. The 2019 European Public Assessment Report for Cufence was also included in the dossier.²¹

The multicentre retrospective study was performed to assess long-term outcomes of treatment with trientine in Wilson's disease patients withdrawn from therapy with penicillamine. Patients were treated for a minimum of six months with trientine (300 mg capsules commercially available from Univar) at doses of 1200 to 2400mg/day (800 to 1600 mg trientine base) in two to four divided doses in adults, or 600 to 1500 mg/day (400 to 1000mg trientine base) in children. 81 patients were enrolled and 77 were included in the intent-to-treat population (4 patients were excluded from the intent-to-treat population as they received non-Univar trientine at initiation). Of the 77 patients, 16 patients (20.8%) were aged < 18 years. Reasons for discontinuation of penicillamine were adverse events (58 (75.3%) patients) or lack of clinical improvement (12 (15.6%) patients). The primary endpoint was investigator rated outcome of hepatic and neurologic symptoms. Efficacy was assessed based on the clinical course (unchanged; improved but not normal; improved to normal; asymptomatic over duration of therapy; worsened) at defined intervals up to 48 months of treatment and then at last visit.

Outcomes reported in Weiss et al. (2018) were:

On average, patients were treated with trientine for 73.3 (\pm 74.76) months. The mean total dose per day during treatment was 1005.7 (\pm 425.32) mg. Treatment with trientine improved hepatic symptoms in 49.4% of patients, with 35.1% asymptomatic, 10.4% unchanged and 5.2% worsened, whereas neurological symptoms remained unchanged in 36.4% of patients, with 46.8% asymptomatic, 14.3% improved and 2.6% worsened.

Weiss et al. (2019) reported outcomes from a prospective study of 52 patients with Wilson's disease, which followed on from the retrospective study. One patient withdrew consent prior to Month 6, so was not included in the full analysis set population. Patients had been treated with trientine for at least 6 months after previous withdrawal from penicillamine. Efficacy was assessed at 6 and 12 months. The primary endpoint was the outcome of hepatic and neurologic symptoms assessed by the investigator. Overall, 50 of 51 patients (98.0%) were responders, while only one patient (2.0%) showed a mild worsening of disease.

In terms of hepatic disease, 25 (49.02%) patients had no hepatic symptoms over the duration of therapy, 8 (15.7%) patients had improved from Baseline at Month 12, 17 (33.3%) patients remained unchanged at month 12, and 1 (2.0%) patient had worsened at month 12. No patients required a liver transplant during the study. In terms of neurologic disease, 24 (47.1%) patients had no neurological symptoms over the duration of therapy, 2 (3.9%) patients improved at month 12, 24 (47.1%) patients remained unchanged at Month 12, and 1 (2.0%) patient had worsened at Month 12.

¹⁹ Weiss, K. H. 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, *J Hepato*, 2018; 68: S106-S107.

²⁰ Weiss, K. H. et al. Safety and Efficacy of Trientine Treatment in Wilson Disease in Patients Withdrawn from D-Penicillamine: Final Results from a Prospective Study, *J Hepatol*, 2019; 70: e383-e624.

²¹ EMA, CHMP, European Assessment Report, Cufence (trientine dihydrochloride), EMA/330602/2019, 29 May 2019. Available from the EMA website.

The authors concluded that treatment with trientine was effective in maintaining stable hepatic and neurologic disease in patients with Wilson's disease. Trientine dihydrochloride was generally safe and well tolerated.

Ala et al. (2015)²²

This was a prospective pilot study to evaluate once-daily trientine in patients with Wilson's disease. 8 patients aged 22 to 71 years with stable Wilson's disease for at least one year on current therapy (zinc acetate, 2; penicillamine, 1; trientine, 5) were prospectively enrolled into a one year trial of trientine at a single daily fixed dose of 15 mg/kg. Patients had clinical and laboratory assessments at monthly intervals for three months before commencing the study, then monthly for three months after commencing the study, then at six, nine and 12 months.

All patients remained clinically well throughout the study, no new neurological signs were detected, and biochemical parameters remained broadly similar. The authors concluded that once-daily trientine should be explored further, and that larger trials and longer-term follow-up are necessary to establish the efficacy and safety of a once-daily regimen.

Appenzeller-Herzog et al. (2019)²³

This was a systematic review and meta-analysis of controlled studies to compare the effectiveness and safety of common therapies for Wilson's disease. Of the 23 studies that met the inclusion criteria, 17 were retrospective observational studies, 3 were prospective observational studies, 2 were non-randomised controlled trials, and 1 was a randomised controlled trial. The control could be placebo, no treatment or any other treatment. A total of 23 studies were included, mostly comparing D-penicillamine to no treatment, zinc, trientine or succimer. One study compared tetrathiomolybdate and trientine. Eleven of 23 studies were of low quality.

The main analyses assessed penicillamine versus no treatment, and penicillamine versus zinc salts. With regard to analyses of trientine, the authors commented:

There were not enough studies comparing other drug combinations to perform meta-analysis. For the comparisons trientine with DPen [D-penicillamine] and trientine with TTM [tetrathiomolybdate], the authors found no difference in effectiveness in primary outcomes. However, they found early neurological deterioration to occur more frequently under therapy with trientine (5/16, 31% or 6/23, 26%) as compared to DPen (8/97, 8%) or TTM (1/25, 4%). At the same time, the relative risk for side effects was found to be lower under trientine therapy (9/38, 24% or 1/23, 4%) compared to DPen (182/295, 62%) or TTM (7/25, 28%).

The authors concluded that high-quality evidence for the comparative effectiveness and safety of Wilson's disease therapies is scarce. All studies but one did not correct for confounding factors, including age, clinical presentation and disease stage. Selection bias was identified as a severe limitation of many of the studies included in this systematic review. Non-uniform definitions of clinical outcomes were also identified as a limitation of the studies.

²² Ala, A. et al. Prospective Pilot Study of a Single Daily Dosage of Trientine for the Treatment of Wilson Disease, *Dig Dis Sci*, 2015; 60: 1433-1439

²³ Appenzeller-Herzog, C. et al. Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies, *Liver Int*, 2019; 39(11): 2136-2152.

Wiggelinkhuizen et al. (2009)²⁴

This was a systematic search of literature addressing treatment in newly presenting patients with Wilson's disease. The review included original studies on clinical efficacy of penicillamine, trientine, tetrathiomolybdate or zinc monotherapy as initial treatment in Wilson disease. None of the 13 studies in this review included trientine treatment. The reported study results were:

Results

One randomized trial and 12 observational studies met the inclusion criteria. These studies were quite heterogeneous and generally of low validity. Nevertheless, according to currently available data, patients with hepatic presentation of Wilson disease are probably most effectively treated by D-penicillamine. Zinc seems to be preferred above D-penicillamine for treatment of presymptomatic and neurological patients, as in these subgroups, the tolerance profile is in favour of zinc, while no obvious differences in clinical efficacy could be observed.

Conclusions

There is lack of high-quality evidence to estimate the relative treatment effects of the available drugs in Wilson disease. Therefore, multicentre prospective randomized controlled comparative trials are necessary.

Safety

The safety dataset is derived from published literature, mostly retrospective and prospective observational studies, and case reports of adverse events. Safety reporting was generally limited and inconsistent across the studies, so the submission did not provide an integrated summary of safety.

Brewer et al. (2006)¹⁶ was a randomised, double-blind, controlled trial comparing trientine to tetrathiomolybdate in the treatment of primarily newly diagnosed patients with neurologic presentation of Wilson's disease. Tetrathiomolybdate is not registered in Australia. Criteria for adverse effects included anaemia (a replicable haemoglobin value < 80% of baseline), leukopenia (a replicable white blood cell count < 80% of baseline), and transaminase elevations consisting of a replicable quadrupling of baseline values of either AST or ALT. One of 23 patients in the trientine arm reported anaemia as an adverse event; 3 of 25 patients in the tetrathiomolybdate arm reported anaemia and/or leukopenia and 4 had further transaminase elevations during 8 weeks of treatment.

In the retrospective study of 405 patients by Weiss et al. (2013)¹² the median follow-up period was 13.3 years. Dosage information was not reported. Discontinuation of treatment due to adverse events (Table 10) was more frequent with penicillamine (94 of 326 (28.8%) treatments) than trientine (10 of 141 (7.1%) treatments, $p = 0.039$). There were no deaths related to adverse events.

²⁴ Wiggelinkhuizen, M. et al. Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease, *Aliment Pharmacol Ther*, 2009; 29(9): 947-958.

Table 10: Weiss et al. (2013) Adverse events leading to discontinuation of treatment

	DPA (n = 326 analyzed)	Trientine (n = 141 analyzed)
Death related to adverse event	0	0
Number of treatments discontinued owing to adverse events	94 (28.8%)	10 (7.1%)
Adverse events leading to discontinuation		
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%)	
Hematuria	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%)

ANA = antinuclear antibody; DPA = D-penicillamine.

Weiss et al. (2019)²⁰ reported safety findings from the prospective study of 52 patients (shown in Table 11).

Table 11: Weiss et al. (2019) Summary of adverse events, and treatment-related adverse events

Occurrence of Adverse Events		Treatment related AEs		
	Trientine 2HCl n (%)		Severity	Trientine 2HCl n (%)
Any TEAE	42 (80.8)	Leukopenia	Moderate	1 (1.9)
Any Serious TEAE	8 (15.4)	Nausea	Mild	1 (1.9)
Any Treatment related AEs	5 (9.6)	Hepatic enzyme increased	Mild	2 (3.8)
Treatment withdrawal due to AE	0	Tremor	Mild	1 (1.9)

2HCl = dihydrochloride; AE = adverse event; TEAE = treatment-emergent adverse event.

In the prospective study published by Ala et al. (2015)²² eight patients were treated with a once-daily dose of trientine (15 mg/kg) for twelve months with no treatment stoppages or drop-outs from the study.

The retrospective study by Scheinberg et al. (1987)¹⁵ did not report any adverse events in the cohort of 13 patients treated with trientine after developing intolerance to penicillamine.

The retrospective study by Dahlman et al. (1995)¹⁷ reviewed 19 patients treated with trientine dihydrochloride 1000 to 1800 mg/day (duration 4 months to 17.5 years), 2 as first-line treatment and 17 following treatment with penicillamine. Colitis was reported in two patients, one of whom also developed duodenitis. No other adverse effects were reported.

Arnon et al. (2007)¹⁸ retrospectively reviewed the records of 22 children with hepatic Wilson's disease treated with trientine dihydrochloride and/or zinc. The children, aged between 7 and 17 years received between 250 and 500 mg trientine twice daily (500 to

1000 mg daily). No significant side effects were observed in any of the patients. Trientine was stopped in one patient after 12 months due to elevated liver enzyme levels, which normalised after zinc dosing was increased.

The retrospective review by Walshe et al. (1982)¹⁴ of 20 penicillamine-intolerant patients treated with trientine dihydrochloride did not report any toxic signs or symptoms relating to treatment with trientine.

Dubois et al. (1990)²⁵ reported clinical experience with seven patients aged 13 to 33 years with Wilson's disease who were treated with trientine following intolerance to penicillamine. The duration of treatment with trientine ranged from six weeks to 16 years, and doses ranged from 500 to 2000 mg/day. No serious adverse effects were reported. In one patient, the initial dose of 1750 mg/day was decreased to 1000 mg/day due to mild thrombocytopenia.

Case reports describing adverse events with trientine are summarised in Table 12.

Table 12: Case reports of adverse events with trientine from the published literature

Reference	Adverse event
Sabolek et al. (2004)	Transient thrombocytopenia (treated with dose reduction)
Chung et al. (2016)	Memory impairments and without Parkinsonian or extrapyramidal signs
Boga et al. (2015)	Drug-induced colitis -resolved on trientine withdrawal and returned on re-challenge
Kim et al. (2013)	Neurological deterioration - resolved on withdrawal of trientine
Harada et al. (2011)	Anaemia and liver dysfunction
Perry et al. (1996)	Secondary acquired sideroblastic anaemia

The submission included published literature reporting use of trientine in pregnancy. Pfeiffenberger et al. (2018)²⁶ reviewed outcomes of 282 pregnancies in 136 women with Wilson's disease treated at three tertiary hospitals between 1965 and 2015. The overall spontaneous abortion rate in the study cohort was 73 of 282 (26%). Patients with an established diagnosis of Wilson's disease receiving medical treatment experienced significantly fewer spontaneous abortions than patients with undiagnosed Wilson's disease (odds ratio, 2.853; 95% confidence intervals (CI) 1.634 to 4.982). Birth defects occurred in 7 of 209 (3%) live births (4 were treated with penicillamine, one with trientine, 2 were not on treatment). The spontaneous abortion rate was lower in women treated with trientine (10 of 36, 28%) than in women with undiagnosed Wilson's disease (35 of 86, 41%).

²⁵ Dubois, R. S. et al. Treatment of Wilson's disease with triethylene tetramine hydrochloride (Trientine), *J Pediatr Gastroenterol Nutr*, 1990; 10(1): 77-81.

²⁶ Pfeiffenberger, J. et al. Pregnancy in Wilson's disease: Management and outcome, *Hepatology*, 2018; 67(4): 1261-1269.

Dathe et al. (2016)²⁷ reported pregnancy outcomes for 3 women treated with trientine throughout pregnancy. One infant had transient bradycardia on days 2 and 3 and elevated blood copper levels. Walshe et al. (1982)¹⁴ reported no evidence of teratogenicity in 6 infants of mothers who became pregnant while taking trientine. Walshe (1986)²⁸ reported outcomes for 11 pregnancies in 8 women with Wilson's disease treated with trientine. Eight pregnancies resulted in the delivery of normal infants. One infant was born premature (31 weeks) and was later shown to have a chromosomal defect, isochromosome X. There was one therapeutic termination and one miscarriage associated with a contraceptive coil.

Risk management plan

The sponsor has submitted Australian risk management plan (RMP) version 0.0 (dated 20 January 2020; data lock point (DLP) 30 November 2019) in support of this application. In the sponsor's response to the clinical evaluators report, an updated Australian-RMP, version 0.1 (dated 25 June 2020; DLP 31 March 2020) was submitted. In the sponsor's response to the first round RMP evaluation report, a further updated Australian RMP, version 0.2 (dated 21 October 2020; DLP 31 March 2020) was submitted. At the third round, the sponsor submitted Australian RMP version 0.4 (dated 22 December 2020; DLP 31 March 2020).

In the sponsor's response to TGA evaluations, the draft PI was updated to change the reference from trientine *hydrochloride* to the *dihydrochloride* salt in line with the Australian Approved Name (AAN).²⁹ The Australian RMP was also updated with the name trientine dihydrochloride in Australian RMP version 0.2. This change does not impact the RMP evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 13 shown below.³⁰

Table 13: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Risk of neurological deterioration during early stages of treatment	Ü	–	Ü	–

²⁷ Dathe K, Beck E, Schaefer C. Pregnancy outcome after chelation therapy in Wilson disease. Evaluation of the German Embryotox Database. *Reprod Toxicol.* 2016;65:39-45.

²⁸ Walshe JM. The management of pregnancy in Wilson's disease treated with trientine. *Q J Med.* 1986;58(225):81-87.

²⁹ Australian Approved Names are a set of generic names approved by the TGA for drugs (chemical entities, including antibiotics) used in Australia.

³⁰ *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Gastrointestinal disturbance	Ü	–	Ü	–
	Iron-deficiency including anaemia	Ü	–	Ü	–
	Zinc-deficiency	Ü	–	Ü	–
	Isolated elevation of liver enzymes	Ü	–	Ü	–
	Increased pregnancy loss	Ü	–	Ü	–
Missing information	Drug exposure during pregnancy	Ü	–	Ü	–
	Use of drugs in lactation and in neonates	Ü	–	Ü	–

- The summary of safety concerns is considered acceptable from an RMP perspective at the third round of evaluation.
- The sponsor has proposed routine pharmacovigilance activities only for all safety concerns. The proposed pharmacovigilance plan is acceptable at the third round. The sponsor has been requested to make some further changes to the pregnancy follow-up form and submit it to the TGA for review at least six weeks prior to launch of the product in Australia.
- The sponsor has proposed routine risk minimisation activities only for all safety concerns. The risk minimisation plan is acceptable at the third round of evaluation.
- There are no new recommendations and one outstanding recommendation. The outstanding recommendation does not impede the decision on this submission.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and Australian-specific annex (ASA). However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The trientine dihydrochloride Australian Risk Management Plan (RMP) (version 0.4, dated 22 December 2020, data lock point 31 March 2020), included with submission PM-2020-00155-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the periodic safety update report (PSUR) requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As the four named Trientine-DRLA, Trientine-RZ, Trientine-Reddy's, Trientine Dr. Reddy's is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Trientine-DRLA, Trientine-RZ, Trientine-Reddy's, Trientine Dr. Reddy's (trientine dihydrochloride) is to be included in the Black Triangle Scheme. The PI and CMI for Trientine-DRLA, Trientine-RZ, Trientine-Reddy's, Trientine Dr. Reddy's must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

Efficacy

Efficacy data for this application are derived from a systematic review of published literature. High quality evidence for the comparative effectiveness and safety of therapies for Wilson's disease is limited. The Levels I and II literature references provide very limited data relevant to the proposed use of trientine in patients intolerant to penicillamine. Retrospective and prospective observational studies provide lower level evidence relevant to the proposed indication.

Weiss et al. (2013)¹² was a retrospective cohort study of 380 patients with Wilson's disease treated at six tertiary care centres in Germany and Austria, and 25 additional patients from the EuroWilson registry.¹³ For trientine in the second-line setting (proposed for registration), 31 of 45 (68.9%) patients with hepatic symptoms showed hepatic improvement, and 26 of 51 (51%) patients with neurologic symptoms showed neurologic improvement. 4 of 45 (8.9%) patients with hepatic symptoms showed hepatic worsening, and 8 of 51 (15.7%) patients with neurologic symptoms showed neurologic worsening. Asymptomatic patients treated with trientine did not show hepatic worsening or neurologic worsening.

There are limitations in the strength of the evidence provided by retrospective studies, as these studies may be subject to bias and uncertainty due to missing information. Weiss et al. (2013)¹² did not report dosages, dose titration, and the formulation of trientine used by patients, no systematic criteria were applied in the initial choice of chelating agent, and neurologic outcomes were not assessed by a standardised or quantitative neurologic scale. Treatment decisions were made according to accepted standards at the time and may have been influenced by confounders. Although there are limitations in the strength of the evidence, Weiss et al. (2013) reviewed the efficacy and safety of penicillamine and trientine in 405 patients treated over a mean duration of 13.3 years. The outcomes support a clinical benefit with trientine in patients who are intolerant of penicillamine. Other retrospective and prospective studies presented in this submission provide data informing use in paediatric patients, supporting the efficacy of trientine in the proposed indication.

Safety

The safety dataset based on published literature is limited, as most of the studies were retrospective reviews reliant on safety information recorded in clinical notes. Many of the studies were small, and safety reporting varied across the studies. Although there are limitations in the safety dataset based on published literature, there is a long history of clinical experience with trientine, including 35 years of marketing authorisation in the USA and UK. Overall, the published literature and the long history of clinical experience support the safety of trientine in the treatment of patients with Wilson's disease who are intolerant of penicillamine.

Labelling

The strength of the proposed product is expressed in terms of the dihydrochloride salt (250 mg) rather than the free base (167 mg). The proposed product was developed as a generic of Syprine 250 mg capsules, and is registered in the USA as Dr Reddy's Trientine Hydrochloride Capsules USP 250 mg. There is a long history of clinical use of Syprine 250 mg capsules internationally, including Australian patients accessing 250 mg capsules through the Special Access Scheme.² Given the familiarity of this product to patients and prescribers, the Delegate was satisfied that the proposed labelling is acceptable.

Switching between different trientine products may present a risk for patients, as different formulations may have a different trientine content and different bioavailability. The draft Product Information (PI) contains a precaution regarding switching between different formulations of trientine. The strength of the product is described in terms of the dihydrochloride salt and the free base in *Section 2 Qualitative and Quantitative Composition*; and *Section 4.2 Dose and Method of Administration* contains a qualifying statement that doses are expressed in terms of trientine dihydrochloride, and that 300 mg of trientine dihydrochloride corresponds to a dose of 200 mg trientine base; however, the Delegate is not satisfied that this statement adequately addresses this issue.

Proposed indication

In the most recent draft PI, the sponsor has rearranged the wording of the indication to:

Trientine dihydrochloride capsules are indicated for the treatment of adults, adolescents and children > 5 years with Wilson's disease in who are intolerant of penicillamine.

The word 'in' has inadvertently been retained following the rearrangement, and should be removed.

The Delegate's preference would be to replace '*adults, adolescents and children > 5 years*' with '*patients*', as paediatric use is appropriately informed by the information in Section 4.4 of the Product Information. This would be consistent with the wording of the sponsor's product in the USA.

The Delegate would be happy to consider the sponsor's position on the following indication:

Trientine dihydrochloride capsules are indicated for the treatment of patients with Wilson's disease who are intolerant of penicillamine.

Deficiencies and limitations of the data

Efficacy and safety data relevant to the proposed indication are derived mostly from retrospective studies, which can be subject to bias and missing information.

The clinical dossier lacks direct linkage between the proposed product and the published literature. Many of the literature references did not specify the trientine product or formulation used in the study.

Proposed conditions of registration

Conditions of registration recommended by the RMP evaluator will be advised in the final RMP evaluation.

Proposed action

There are limitations in the efficacy and safety data provided from published literature, but there is a long history of clinical experience with trientine, including 35 years of marketing authorisation internationally. The use of trientine as a chelating agent in patients with Wilson's disease is recommended in clinical practice guidelines internationally, including the Australian Therapeutic Guidelines.³¹

Wilson's disease is a rare disease which is managed by specialists with expertise in the treatment of the condition. Treatment options are limited in patients who are intolerant of penicillamine. The clinical consequences of untreated or inadequately treated disease are severe, and include hepatic failure, neurologic impairment and death. In this context, the clinical studies presented in this literature-based submission adequately support the efficacy and safety of trientine dihydrochloride for the treatment of patients with Wilson's disease who are intolerant of penicillamine.

There are no outstanding clinical issues requiring expert advice from Advisory Committee on Medicines (ACM).

The Delegate had no reason to say, at the time, that the application for Trientine Dr.Reddy's, Trientine-Reddy's, Trientine-RZ, and Trientine DRLA should not be approved for registration.

Advisory Committee considerations³²

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

³¹ Y&TG complete. Melbourne: Therapeutic Guidelines Ltd; 2019. Wilson disease (updated March 2017; cited 8 November 2019).

³² The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: <https://www.tga.gov.au/committee/advisory-committee-medicines-acm>.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Trientine Dr.Reddy's, Trientine-Reddy's, Trientine-RZ, and Trientine-DRLA (trientine dihydrochloride) 250 mg, capsule, bottle indicated for:

Trientine dihydrochloride capsules are indicated for the treatment of patients with Wilson's disease who are intolerant of penicillamine.

Specific conditions of registration applying to these goods

- Trientine-DRLA, Trientine-RZ, Trientine-Reddy's, Trientine Dr. Reddy's (trientine dihydrochloride) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Trientine-DRLA, Trientine-RZ, Trientine-Reddy's, Trientine Dr. Reddy's must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The trientine dihydrochloride Australian Risk Management Plan (RMP) (version 0.4, dated 22 December 2020, data lock point 31 March 2020), included with submission PM-2020-00155-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the European Union (EU) during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Trientine Dr.Reddy's, Trientine-Reddy's, Trientine-RZ, and Trientine-DRLA approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<https://www.tga.gov.au>