▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – TRIENTINE DR. REDDY'S (TRIENTINE DIHYDROCHLORIDE) CAPSULES

1 NAME OF THE MEDICINE

Trientine dihydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules containing 250 mg of trientine dihydrochloride, equivalent to 167 mg trientine base . Capsules also contain gelatin. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

TRIENTINE DR. REDDY'S, trientine dihydrochloride capsules, 250 mg, are yellow opaque, hard gelatin size "1" capsules imprinted with "RDY" on cap and "459" on body in black ink filled with white to pale yellow powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Systematic evaluation of dose and/or interval between dose has not been done. However, based on clinical experience, the recommended initial doses of trientine dihydrochloride capsules are given below.

The doses are expressed in terms of trientine dihydrochloride and the equivalent dose of trientine free base. It should be noted that a dose of 250mg trientine dihydrochloride corresponds to a dose of 167mg trientine free base. This should be considered if a patient is transferred from one trientine formulation to another.

Children > 5 years

500 to 750 mg trientine dihydrochloride /day (2 to 3 capsules) given in divided doses two or three times daily. This may be increased to a maximum of 1,500 mg/day for children aged > 5 years. The paediatric dosage *in terms of trientine free base* is 333 to 500 mg/day to a maximum of 1000mg/day.

The initial dose for children > 5 years can be expressed on a weight basis as 20mg/kg body weight trientine dihydrochloride in 2-3 divided doses, rounded up to the nearest number of whole capsules

Adults

750 to 1,250 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 2,000 mg/day for adults. The adult dosage *in terms of trientine free base* is 500 to 833 mg/day to a maximum of 1333 mg/day.

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 microgram/dL (3.1 micromol/L). Optimal long-term maintenance dosage should be determined at 6 to 12 month intervals (see 4.4 Special Warnings And Precautions For Use; Effects on Laboratory Tests).

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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients receiving trientine dihydrochloride capsules should remain under regular medical supervision throughout the period of drug administration. Patients (especially women) should be closely monitored for evidence of iron deficiency anaemia..

Caution is advised when switching a patient from another trientine formulation. Different trientine salts are available which may have a different trientine content (base) and dose adjustment may be required (see Section 4.2 Dose and Method of Administration).

Trientine is a chelating agent that has been found to reduce serum iron levels. Iron supplementation may be necessary in some cases and concomitant oral iron should be administered at a different time than trientine (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

The combination of trientine with zinc is not recommended.

There is no evidence that calcium and magnesium antacids alter the efficacy of trientine but it is recommended to separate their administration (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

In patients who were previously treated with D-Penicillamine, lupus-like reactions have been reported during subsequent treatment with trientine, however it is not possible to determine if there is a causal relationship with trientine.

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.

Monitoring

Patients receiving trientine should remain under regular medical supervision and be monitored using all available clinical data for appropriate control of clinical symptoms and copper levels in order to optimise treatment. Frequency of monitoring is recommended to be at least twice a year. More frequent monitoring is advised during the initial phase of treatment and during phases of disease progression or when dose adjustments are made as to be decided by the treating physician (see Section 4.2 Dose and Method of Administration).

The aim of maintenance treatment is to maintain free copper levels in plasma (also known as non- ceruloplasmin plasma copper) and the urinary copper excretion within the acceptable limits. The normal level of free copper in the serum is usually 10 to 15 microgram/dL (1.5 – 2.3 micromol/L). The determination of serum free copper, calculated using the difference between the total copper and the ceruloplasmin-bound copper can be a useful index for monitoring therapy.

The measurement of copper excretion in the urine may be performed during therapy as a useful measure of treatment compliance.

Like with all anti-copper agents, overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women (see Section 4.6 Fertility, Pregnancy and Lactation) since copper is required for proper growth and mental development. Monitoring for manifestations of overtreatment should be undertaken.

Iron and zinc levels should be monitored in view of the known chelating effects of trientine on these minerals and the relative frequent reports of iron-deficiency, including anaemia. Any treatment with iron or zinc should be timed separately from trientine dosing.

Patients with renal and/or hepatic impairment receiving trientine should remain under regular medical supervision for appropriate control of symptoms and copper levels. Close monitoring of renal and/or liver function is also recommended in these patients (see Section 4.2 Dose and Method of Administration). Some liver enzyme elevations may be related to the use of trientine.

Worsening of neurological symptoms may occur at the beginning of chelation therapy due to excess of free serum copper during the initial response to treatment. It is possible that this effect may be more evident in patients with pre-existing neurological symptoms. It is recommended to monitor patients closely for such signs and symptoms and to consider careful titration to reach the recommended therapeutic dose and to reduce dose when necessary.

Dose adjustments in the trientine dose should be considered in case of signs of reduced efficacy such as (persistent) increase in liver enzymes, and worsening of tremor. When trientine doses are adjusted this should be done in small steps. The trientine dose may also be reduced in case of side effects of trientine, such as gastrointestinal complaints and haematological changes. Trientine doses should be reduced to a more tolerable dose and may be increased again, once side effects have been resolved.

Long term treatment with trientine at high doses (>2400mg) may result in over-chelation.

Use in hepatic impairment

There is limited information in patients with hepatic impairment. No specific dose adjustment is required in these patients (see Section 4.4 Special Warnings and Precautions for Use).

Use in renal impairment

There is limited information in patients with renal impairment. No specific dose adjustment is required in these patients (see Section 4.4 Special Warnings and Precautions for Use).

Patients with renal impairment receiving trientine should remain under regular medical supervision for appropriate control of symptoms and copper levels. Close monitoring of renal function is also recommended in these patients (see Section 4.2 Dose and Method of Administration).

Use in the elderly

Clinical studies of trientine dihydrochloride capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Paediatric use

The safety and efficacy of trientine in children aged < 5 years have not been established. The pharmaceutical form is not suitable for administration to children < 5 years.

Effects on laboratory tests

No information available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Trientine has been found to reduce serum iron levels, possibly by reducing its absorption, and iron supplements may be required. Since iron and trientine may inhibit absorption of each other, iron supplements or other heavy metals should be taken after at least two hours have elapsed from the administration of trientine.

No specific food interaction studies in humans have been performed with trientine. However as trientine is poorly absorbed following oral intake, food may inhibit absorption. The principal mechanism of action of trientine requires its systemic exposure (see Section 5.1 Pharmacodynamic Properties) so it is recommended that trientine be taken at least 1 hour before meals or 2 hours after meals and at least one hour apart from any other medicinal product, food, or milk to allow for maximum absorption and reduce the likelihood of the formation of complexes by metal binding in the gastrointestinal tract (see Section 4.2 Dose and Method of Administration).

Although there is no evidence that calcium or magnesium antacids alter the efficacy of trientine, it is good practice to separate their administration.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

It is unknown whether trientine has an effect on human fertility.

Use in pregnancy – Pregnancy Category D

Trientine dihydrochloride was teratogenic in animals at clinically-relevant doses, possibly due to the induction of copper deficiency or zinc toxicity. Fetal brain abnormalities like haemorrhages and haematomas, delayed ossification in the cranium, exencephaly, microcephaly, and hydrocephaly have been observed in mice and rats treated with trientine.

There are no adequate and well-controlled studies in pregnant women. Trientine dihydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Since copper is required for proper growth and mental development, dose adjustments may be required to ensure that the fetus will not become copper deficient and close monitoring of the patient is essential (see Section 4.4 Special Warnings and Precautions for Use).

The pregnancy should be closely monitored in order to detect possible fetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range.

Babies born to mothers being treated with trientine should be monitored for serum copper levels where appropriate.

Use in lactation.

It is not known whether trientine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trientine dihydrochloride is administered to a nursing mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Nausea can commonly occur on initial treatment and occasionally skin rash can occur. Duodenitis and severe colitis have been reported; gastrointestinal disorders are possibly related to higher doses of trientine.

There have been reports of neurological deterioration at the start of treatment in Wilson's disease patients treated with copper chelators including trientine, with symptoms of dystonia, rigidity, tremor and dysarthria (see Section 4.4 Special Warnings and Precautions for Use).

No clinical studies have included a systematic evaluation of adverse effects of trientine, however clinical experience over many years supports that it is well tolerated in the treatment of patients

with Wilson's Disease, with adverse events reported less frequently for trientine than for D-penicillamine therapy.

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

MedDRA – SOC database	Adverse reaction
Blood and lymphatic disorders	Uncommon: anaemia, aplastic anaemia, sideroblastic anaemia
Nervous system disorders	Uncommon: dystonia, tremor Not known: dysarthria, muscle rigidity, neurological deterioration
Immune system disorders	Not known: Lupus-like syndrome, lupus nephritis
Gastrointestinal disorders	Common: nausea Not known: colitis; duodenitis
Skin and subcutaneous disorders	Uncommon: rash

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Occasional cases of trientine overdose have been reported. A large overdose of 40 g of trientine base resulted in self- limiting dizziness and vomiting with no other clinical sequelae or significant biochemical abnormalities reported (Hashim & Parnell, 2015).

There is no antidote for trientine acute overdose.

Chronic high dose trientine treatment can lead to copper deficiency and reversible sideroblastic anaemia. A patient who received 2500mg trientine /day for about 10 years was reported to have copper depletion and the consequent decrease of copper-binding holo-ceruloplasmin induced anemia, iron deposition and liver function abnormality in the patient (Harada et al, 2011).

Overtreatment and excess copper removal can be monitored using values of urine copper excretion and of non-ceruloplasmin bound copper. Close monitoring is required to optimise the dose or to adapt treatment if necessary (see Section 4.4 Special Warnings and Precautions for Use).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Wilson's disease (hepatolenticular degeneration) is an autosomal inherited metabolic defect resulting in an inability to maintain a near-zero balance of copper. Excess copper accumulates possibly because the liver lacks the mechanism to excrete free copper into the bile. Hepatocytes store excess copper but when their capacity is exceeded copper is released into the blood and is taken up into extrahepatic sites. This condition is treated with a low copper diet and the use of chelating agents that bind copper to facilitate its excretion from the body (Hedera et al, 2019).

Trientine is a copper-chelating agent whose principal mechanism of action is to eliminate absorbed copper from the body by forming a stable complex that is then eliminated through urinary excretion. Trientine may also chelate copper in the intestinal tract and so inhibit copper absorption.

Clinical trials

The efficacy of trientine was assessed based on published literature reports. The key study in patients with Wilson's Disease who were intolerant to D-penicillamine was a retrospective analysis conducted by Weiss et al, 2013 on 380 patients treated at six tertiary care centres in Germany and Austria, and 25 additional patients from the EUROWILSON registry. In this population 141 patients had received trientine, 103 received trientine as second line therapy. Around one third of all patients with hepatic WD and more than two thirds of symptomatic patients showed hepatic improvement with second-line trientine. About one quarter of all neurologic WD patients and half of symptomatic patients showed neurological improvement. Adverse events leading to discontinuation of treatment were more frequent for patients receiving D-penicillamine than trientine (p=0.039). (Weiss et al, 2013)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absorption of trientine following oral administration is low and variable (Kodama et al, 1993). The pharmacokinetic profile of Dr Reddy's trientine formulation has been evaluated in Study 15-vin-474 after a single oral dose of 250mg trientine in healthy male and female subjects under fasting conditions.

Plasma levels of trientine rose rapidly following administration with the median peak level (C_{max} 558.5 ± 219.5 ng/mL) reached at T_{max} of 1.25 hours. The trientine plasma concentration then declined in a multiphasic manner, initially rapidly, followed by a slower elimination phase.

Distribution

A reported central volume of distribution (V_d) for trientine of 393 L and peripheral volume of 252 L indicates that trientine is widely distributed in tissues, with relatively high concentrations measured in the liver, heart and kidney of rats (Cho et al, 2009).

Metabolism

Trientine is acetylated in two majors metabolites, N_1-acetyltriethylenetetramine (MAT) and N_1, N_{10}-diacetyltriethylenetetramine (DAT) (Liu et al, 2007). MAT and DAT are capable of chelating

copper, albeit with a lower affinity than trientine. The extent of the contribution of MAT and DAT to the overall effect of trientine on copper levels in Wilson's Disease patients remains to be determined.

Excretion

Trientine and its metabolites are rapidly excreted in the urine, although low levels of trientine could still be detected in the plasma after 20 hours. Study 15-vin-474 reported the elimination half life ($T_{1/2)\,of}$ 10.2 ± 6.1 hours and an elimination constant (K_{el}) of 0.09 ± 0.06 L/hr.

In healthy adults and in WD patients, the renal excretion of trientine and its metabolites accounts for a small percentage of total trientine dose. Population PK modelling, based on data collected from healthy volunteers with normal renal function suggests that the clearance of trientine may be partially dependent on GFR (Cho et al, 2009).

Unabsorbed trientine is bound to intestinal copper and eliminated through faecal excretion (Cho et al, 2009).

Linearity/non-linearity

Plasma exposures in humans have shown a linear relationship with oral doses of trientine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Trientine has shown positive effects in *in vitro* genotoxicity studies, including the Ames test and genotoxicity tests in mammalian cells. *In vivo*, trientine was however negative in the mouse micronucleus test.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TRIENTINE DR. REDDY'S capsules contain colloidal silicon dioxide, ferric oxide yellow, gelatin, magnesium stearate, polyethylene glycol, titanium dioxide and purified water as inactive ingredients. The imprinting ink (TekPrint™SW-9008 Black Ink) contains black iron oxide, potassium hydroxide, propylene glycol and shellac.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Keep container tightly closed. Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottle with child-resistant screw cap, in packs of 100.

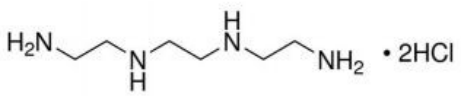
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Trientine dihydrochloride is N,N'-bis (2-aminoethyl)-1,2-ethanediamine dihydrochloride. It is a white to pale yellow powder. It is soluble in methanol and freely soluble in water.

Chemical structure



CAS number

38260-01-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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Melbourne, VIC, 3004, Australia
Phone: 1800 733 397

9 DATE OF FIRST APPROVAL

29 March 2021

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

REFERENCES:

Cho H-Y., Blum R.A., Sunderland T., et al. *Journal of Clinical Pharmacology. 49 (8) (pp 916-928), 2009*

Kodama H., Meguro Y., Tsunakawa A., et al. *Tohoku Journal of Experimental Medicine. 169 (1) (pp 59-66), 1993*

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Hedera P. *Parkinsonism and Related Disorders. 59 (pp 140-145), 2019*

Lu J., Chan Y.-K., Gamble G.D., Poppitt S.D., et al. *Drug Metabolism and Disposition. 35 (2) (pp 221-227), 2007*

Weiss K.H., Thurik F., Gotthardt D.N., et al. *Clinical Gastroenterology and Hepatology. 11 (8) (pp 1028-1035), 2013*