▼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 WAYMADE (TRIENTINE DIHYDROCHLORIDE) CAPSULES

1 NAME OF THE MEDICINE

Trientine dihydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg trientine dihydrochloride (equivalent to 166.7 mg trientine base).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Cylindrical size “1” hard gelatin capsule with opaque orange colour cap printed with “NAV” in black ink and opaque white colour body printed with “101” in black ink. Capsule filled with white to off white colour powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Trientine Waymade is indicated in the treatment of patients with Wilson’s disease who are intolerant of penicillamine.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The starting dose would usually correspond to the lowest recommended dose and the dose should subsequently be adapted according to the patient’s clinical response (see section 4.4 Special Warnings and Precautions for Use).

The daily dose of Trientine Waymade should be increased only when the clinical response is not adequate, or the concentration of free serum copper is persistently above 3.1micromol/L. Optimal long-term maintenance dosage should be determined at 6-12 month intervals.

Adults

The recommended initial dose of Trientine Waymade is 750-1250 mg/day (equivalent to 500-833 mg/day trientine base) for adults given in divided doses two, three or four times daily. This may be increased to a maximum of 2000 mg/day (1333 mg/day trientine base) for adults.

Paediatric patients

The recommended initial dose of Trientine Waymade is 20 mg/kg/day (equivalent to 13 mg/kg/day trientine base) rounded off to the nearest 250 mg, given in two or three divided doses. This may be increased to a maximum of 1500 mg/day (equivalent to 1000 mg/day trientine base) for paediatric patients age 12 or under.

Patients primarily presenting hepatic symptoms

The recommended dose in patients primarily presenting hepatic symptoms is the same as the recommended adult dose. It is advised, however, to monitor patients presenting with hepatic symptoms every two to three weeks after initiation of treatment with Trientine Waymade.

Patients primarily presenting neurological symptoms

Dose recommendations are the same as for adults. However, up titration should be done with moderation and consideration, and adapted according to the patient's clinical response such as worsening of tremor as patients could be at risk of neurological deterioration at initiation of treatment (see section 4.4 Special Warnings and Precautions for Use). It is further advised to monitor patients presenting with neurological symptoms every one to two weeks after initiation of treatment with Trientine Waymade until target dose is reached.

Method of administration

The capsules should be swallowed whole with water and should not be opened or chewed.

It is important that Trientine Waymade 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 medicine, food, or milk. This permits maximum absorption and reduces the likelihood of inactivation of the drug by metal binding in the gastrointestinal tract.

Because of the potential for contact dermatitis, any site of exposure to the capsule contents should be washed with water promptly.

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

When switching a patient from another trientine formulation, caution is advised because different trientine salts are available which may have a different trientine content (base) and a different bioavailability. Dose adjustment may be required (see section 4.2 Dose and method of administration).

Trientine dihydrochloride is not indicated as an alternative to penicillamine in the treatment of rheumatoid arthritis or cystinuria. Penicillamine-induced systemic lupus erythematosus may not resolve on transfer to Trientine Waymade.

Trientine dihydrochloride is a chelating agent which has been found to reduce serum iron levels possibly reducing its absorption. Iron supplementation may be necessary in some cases and should be administered at a different time of the day to Trientine Waymade.

There is no evidence that calcium or magnesium antacids alter the efficacy of trientine but it is good practice to separate their administration. (i.e. antacids should be taken after meals). See section 4.5 Interactions with other medicines and other forms of interactions.

There is no advantage in using trientine and penicillamine in combination.

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 nonceruloplasmin plasma copper) and the urinary copper excretion within the acceptable limits.

The determination of serum free copper, calculated using the difference between the total copper and the ceruloplasmin-bound copper (normal level of free copper in the serum is usually 1.6 to 2.4 micromol/L) can be a useful index for monitoring therapy.

The measurement of copper excretion in the urine may be performed during therapy. Since chelation therapy leads to an increase in urinary copper levels, this may/will not give an accurate reflection of the excess copper load in the body but may be a useful measure of treatment compliance.

The use of appropriate copper parameter target ranges is described in clinical practice guidelines related to Wilson's disease.

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. Therefore, monitoring for manifestations of overtreatment should be undertaken.

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).

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.

Use in the elderly

Clinical studies of trientine dihydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience is insufficient to determine differences in responses between the elderly and younger patients. 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

Controlled studies of the safety and effectiveness of **t**rientine dihydrochloride in paediatric patients have not been conducted. It has been used clinically in paediatric patients as young as 6 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Zinc

There are insufficient data to support the concomitant use of zinc and trientine. The combination of trientine with zinc is not recommended as interaction of zinc with trientine is likely, thereby reducing the effect of both active substances.

Other anti-copper agents

No interaction studies have been performed on the concomitant administration of trientine with penicillamine.

Food

Trientine is poorly absorbed following oral intake and food further inhibits trientine absorption. Specific food interaction studies have been performed with trientine in healthy subjects, showing a reduction of the extent of absorption of trientine up to 45%. Systemic exposure is critical for its principal mechanism of action, copper chelation (see section 5.1 Pharmacodynamic properties). Therefore, it is recommended that trientine is 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).

Other products

Trientine has been found to reduce serum iron levels. Therefore, iron supplementation may be necessary in some cases. Concomitant oral iron or other heavy metals should be administered at a different time than trientine to prevent the formation of complexes (see section 4.4 Special warnings and precautions for use).

There is no evidence that calcium and magnesium antacids alter the efficacy of trientine but it is recommended to separate their administration.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

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 Waymade should be used during pregnancy only if the potential benefit justified the potential risk to the fetus.

If used in pregnancy, careful monitoring of maternal serum copper levels is required, and the dose of trientine adjusted as required to maintain serum copper levels within the normal range.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been identified which evaluated the impact of trientine on the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial experience

Weiss 2013[i] reported 7.1% (10/141) patients receiving trientine discontinued due to adverse events which was statistically lower than 28.8% (94/326) for penicillamine (p=0.039). The most frequent adverse events associated with discontinuation of trientine treatment were: arthralgia (n=4), gastric complaints such as nausea and gastric pain (n=2), pruritus, myalgia, nephropathy, leukopenia, increase in antinuclear antibodies, erythema, lupus erythematosus, hirsutism (n=1 for each) and other non-specified adverse events (n=4).

A significantly higher rate of neurologic deterioration was reported for symptomatic patients with neurological presentations who received first-line treatment with trientine (4/20, 20%) than penicillamine (6/114, 5.3%) (p=0.042), although the differences were not significant (p=0.672) for second-line treatments with trientine and penicillamine (8/51, 15.7% and 1/13, 7.3%, respectively). The rate of hepatic deterioration for symptomatic patients with hepatic presentations was not significantly different between trientine and penicillamine treatments.

Tabulated list of adverse reactions

Table 1 presents the list of adverse reactions according to the MedDRA system organ classification. 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).

Table 1. List of adverse reactions

System organ class and frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon	Anaemia, aplastic anaemia, sideroblastic anaemia
Nervous system disorders	
Uncommon	Dystonia, tremor
Not known	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 tissue disorders	
Uncommon	Rash

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, for example, dystonia, rigidity, tremor and dysarthria (see section 4.2 Dose and method of administration).

Paediatric population

Clinical trials including a limited number of children in the age range of 5-17 years at the start of treatment indicate that frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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

There is a report of an adult woman who ingested 30 grams of trientine dihydrochloride without apparent ill effects. In a second case, a large overdose of trientine (40 g; 200 tablets) resulted in self-limiting dizziness and vomiting with no further clinical sequelae or significant biochemical abnormalities.

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

Trientine has a structure similar to polyamines and chelates copper by forming a stable complex with the four constituent nitrogens in a planar ring. The pharmacodynamic action of trientine is dependent on its property of chelating copper and elimination of the trientine-copper complex in the urine. Trientine may also chelate copper in the intestinal tract and in the process inhibit copper absorption.

Clinical Trials

Weiss 2013[i] conducted a multicentre, retrospective observational study to compare the efficacy and safety of trientine versus penicillamine (DPA) in patients with WD (n=380) treated at tertiary care centres in Germany and Austria, and additional patients from the EUROWILSON registry (n=25). The cohort consisted of outcomes for patients with WD treated with DPA (n=326) and trientine (n=141) for at least six months. The primary efficacy outcome was the change in hepatic and neurologic outcomes (i.e. clinical symptoms and tests) at 6, 12, 24, 36, and 48 months after initiation of the treatment regimen. Hepatic outcome measures were based on clinical symptoms, course of liver enzymes, and liver function tests. Patients with either of these clinical or biochemical signs of liver disease were considered symptomatic. The course of neurologic disease was evaluated by the physician.

Stable hepatic disease under second-line therapy was reported for 4 of 16 (25%) penicillamine treatments and for 10 of 45 (22.2%) trientine treatments. No hepatic worsening was seen in chelation monotherapy for patients who presented without hepatic symptoms. A higher rate of hepatic improvement was observed for second-line therapy when symptomatic patients were considered of all patients with hepatic presentation (31/45, 68.9% versus 31/103, 30.1%).

Stable neurologic disease for second-line therapy was reported for 9 of 13 (69.2%) d-penicillamine treatments and for 17 of 51 (33.3%) trientine treatments. With second-line therapy, neurologic worsening was comparable between groups, with a trend favoring penicillamine (penicillamine: 1 of 13, 7.3%; trientine: 8 of 51, 15.7%). No statistically significant differences were found for the rate of improvement for second-line (penicillamine 3 of 13, 23.1% versus trientine 26 of 51, 51%) chelation therapy.

There were no differences between the treatments based on the number of overall discontinuations (p=0.36) with 142/326 (43.6%) discontinuing from penicillamine and 36/141 (25.5%) from trientine therapy. Discontinuation as a result of adverse events was

more frequent for penicillamine treatment than for trientine treatment with 94/326 (28.8%) of DPA treatments stopped because of adverse events versus 10/141 (7.1%) of trientine treatments (p=0.039).

Chelating Properties

Preclinical Studies

Studies in animals have shown that trientine dihydrochloride has cupriuretic activities in both normal and copper-loaded animals.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, trientine absorption is low and variable in patients with Wilson's disease. Trientine is absorbed with T_{max} occurring between 0.5 and 4 hours post-dose in healthy volunteers and patients. Exposure seems to be highly variable between subjects. The terminal half-life in plasma is approximately 13.5 h.

Distribution

Trientine is widely distributed in tissues with relatively high concentrations measured in the liver, heart, and kidney in the rat.

Metabolism

Trientine is acetylated in two major metabolites, N_1-acetyltriethylenetetramine (MAT) and N_1,N_{10}-diacetyltriethylenetetramine (DAT). MAT and DAT are capable of chelating copper, albeit with a lower affinity than trientine. However, the extent of MAT and DAT's contribution 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. Unabsorbed trientine is eliminated through faecal excretion.

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

- stearic acid
- gelatin
- titanium dioxide
- sunset yellow FCF
- purified water
- TekPrint SW-9008 Black Ink

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 at 2° to 8°C (Refrigerate. Do not freeze).

Store in the original container and retain the silica gel sachet in the bottle in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

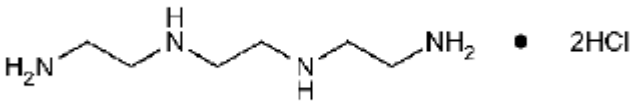
100 capsules in a white HDPE bottle with a cap with screw cap, also containing a sachet of dried silica gel as desiccant.

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

Chemical structure



CAS number

38260-01-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Waymade Australia Pty Ltd
KPMG Tower 3 International Towers
300 Barangaroo Avenue
Sydney NSW 2000

9 DATE OF FIRST APPROVAL

11th January 2021

10 DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
	New Product

[i] Weiss K H, Thirik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson Disease. Clin Gastroenterol Hepatol. 2013; 11:1028-1035