NEW ZEALAND DATA SHEET

1 TRIENTINE WAYMADE 250mg CAPSULES

Trientine Waymade 250 mg oral capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg trientine dihydrochloride.

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

Dose

Adults and children

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 recommended initial dose of Trientine Waymade is 500 -750 mg/day for paediatric patients and 750 -1250 mg/day for adults given in divided doses two, three or four times daily. This maybe increased to a maximum of 2000 mg/day for adults or 1500 mg/day for paediatric patients age 12 or under.

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 20 mcg/dL. Optimal long-term maintenance dosage should be determined at 6 to 12 month intervals.

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

Trientine dihydrochloride is not indicated as an alternative to D-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.

There have been reports of neurological deterioration in Wilson's Disease patients treated with copper chelators including trientine. It is possible this effect may be more evident in patient with pre-existing neurological symptoms. It is recommended to monitor patients closely for such signs and symptoms and to consider a titrated increase in dose to reach the recommended therapeutic dose.

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 population

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 with no reported adverse experiences.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

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.

Calcium and magnesium antacids

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

Mineral supplements

In general, mineral supplements should not be given since they may block the absorption of trientine dihydrochloride. However, iron deficiency may develop, especially in children and menstruating or pregnant women, or as a result of the low copper diet recommended for Wilson's disease. If necessary, iron may be given in short courses, but since iron and trientine dihydrochloride each inhibit absorption of the other, two hours should elapse between administration of trientine dihydrochloride and iron.

Food

It is important that trientine dihydrochloride be taken 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. This permits maximum absorption and reduces the likelihood of inactivation of the drug by metal binding in the gastrointestinal tract.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy

Pregnancy Category B3

Trientine dihydrochloride was teratogenic in some animal models at higher than the human dose, possibly due to the induction of copper deficiency or zinc toxicity. 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 Undesirable effects

Summary of the safety profile

Nausea on initial treatment and occasionally skin rash can occur. Duodenitis and severe colitis have been reported. Neurological deterioration can occur at the start of the treatment.

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

Description of selected adverse reactions

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 to 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 https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Trientine dihydrochloride is a copper-chelating agent which aids the elimination of copper from the body by forming a stable soluble complex that is readily excreted from the kidney. Trientine may also chelate copper in the intestinal tract and so inhibit copper absorption.

Trientine is a chelator with a polyamine-like structure and copper is chelated by forming a stable complex with the four constituent nitrogens in a planar ring. Thus, the pharmacodynamic action of trientine is dependent on its chemical property of chelating copper and not on its interaction with receptors, enzyme systems or any other biological system that might differ between species. Trientine may also chelate copper in the intestinal tract and so inhibit copper absorption.

Clinical Trials

Weiss 2013[1] 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.

In symptomatic hepatic patients, comparable rates of improvement were observed under first line d-penicillamine therapy (185 of 204; 90.7%) and first-line trientine therapy (25 of 27; 92.6%). In the same group, stable hepatic disease in terms of unchanged hepatic symptoms was observed for first-line d-penicillamine therapy treatment in 15 of 204 (7.4%) treatments versus 2 of 27 (7.4%) in the trientine group. Stable hepatic disease under second-line therapy was reported for 4 of 16 (25%) d-penicillimine 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. No statistically significant differences were found for the rate of

1 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.

improvement for first-line (d-penicillamine 77 of 114, 67.5% versus trientine 11 of 20, 55%) or second-line (d-penicillamine 3 of 13, 23.1% versus trientine 26 of 51, 51%) chelation therapy.

Stable neurologic disease was observed for first-line in the d-penicillamine group in 31 of 114 (27.2%) treatments versus 5 of 20 (25%) in the trientine group. 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 d-penicillamine (d-penicillamine: 1 of 13, 7.3%; trientine: 8 of 51, 15.7%). A significantly higher rate of neurologic worsening was reported for first-line therapies of symptomatic neurologic patients treated with trientine (4 of 20; 20%) versus d-penicillamine (6 of 114; 5.3%) (p=0.042).

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

Forty-one patients (18 male and 23 female) between the ages of 6 and 54 with a diagnosis of Wilson's disease and who were intolerant of d-penicillamine were treated in two separate studies with trientine dihydrochloride. The dosage varied from 450 to 2400 mg per day. The average dosage required to achieve an optimal clinical response varied between 1000 mg and 2000 mg per day. The mean duration of trientine dihydrochloride therapy was 48.7 months (range 2-164 months). Thirty-four of the 41 patients improved, 4 had no change in clinical global response, 2 were lost to follow-up and one showed deterioration in clinical condition. One of the patients who improved while on therapy with trientine dihydrochloride experienced a recurrence of the symptoms of systemic lupus erythematosus which had appeared originally during therapy with penicillamine. Therapy with trientine dihydrochloride was discontinued. No other adverse reactions, except iron deficiency, were noted among any of these 41 patients.

One investigator treated 13 patients with trientine dihydrochloride following their development of intolerance to d-penicillamine. Retrospectively, the investigator compared these patients to an additional group of 12 patients with Wilson's disease who were both tolerant of and controlled with d-penicillamine therapy, but who failed to continue any copper chelation therapy. The mean age at onset of disease of the latter group was 12 years as compared to 21 years for the former group. The trientine dihydrochloride group received d-penicillamine for an average of 4 years as compared to an average of 10 years for the non-treated group.

Various laboratory parameters showed changes in favor of the patients treated with trientine dihydrochloride. Free and total serum copper, SGOT and serum bilirubin all showed mean increases over baseline in the untreated group which were significantly larger than with the patients treated with trientine dihydrochloride. In the 13 patients treated with trientine dihydrochloride, previous symptoms and signs relating to d-penicillamine intolerance disappeared in 8 patients, improved in 4 patients, and remained unchanged in one patient. The neurological status in the trientine dihydrochloride group was unchanged or improved over baseline, whereas in the untreated group, 6 patients remained unchanged and 6 worsened. Kayser-Fleischer rings improved significantly during trientine dihydrochloride treatment.

The clinical outcome of the two groups also differed markedly. Of the 13 patients on therapy with trientine dihydrochloride (mean duration of therapy 4.1 years; range 1 to 13 years), all were alive at the data cutoff date, and in the non-treated group (mean years with no therapy 2.7 years; range 3 months to 9 years), 9 of the 12 died of hepatic disease.

Chelating Properties

Preclinical Studies

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

Human Studies

Renal clearance studies were carried out with penicillamine and trientine dihydrochloride on separate occasions in selected patients treated with penicillamine for at least one year. Six-hour excretion rates of copper were determined off treatment and after a single dose of 500 mg of penicillamine or 1.2 g of trientine dihydrochloride. The mean urinary excretion rates of copper were as follows:

No. of Patients	Single Dose Treatment	Basal Excretion Rate (µg Cu + + /6hr)	Test-dose Excretion Rate (µg Cu + + /6hr)
6	Trientine, 1.2 g	19	234
4	Penicillamine, 500 mg	17	320

In patients not previously treated with chelating agents, a similar comparison was made:

No. of Patients	Single Dose Treatment	Basal Excretion Rate (µg Cu + + /6hr)	Test-dose Excretion Rate (µg Cu + + /6hr)
8	Trientine, 1.2 g	71	1326
7	Penicillamine, 500 mg	68	1074

These results demonstrate that trientine dihydrochloride is effective as a cupriuretic agent in patients with Wilson's disease although on a molar basis it appears to be less potent or less effective than penicillamine. Evidence from a radio-labelled copper study indicates that the different cupriuretic effect between these two drugs could be due to a difference in selectivity of the drugs for different copper pools within the body.

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 has low human plasma protein binding and 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, N1-acetyltriethylenetetramine (MAT) and N_1,N_{10}-diacetyltriethylenetetramine (DAT). 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
- water - purified
- 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

36 months

6.4 Special precautions for storage

Keep container tightly closed.

Store below 25°C.

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

Once opened, Trientine Waymade capsules should be stored in the original container and used within 60 days.

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

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Clinect NZ Pty Limited c/- Ebos Group Limited

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Christchurch 8024

New Zealand

Telephone: 0800 138 803

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine:

9 December 2021

10 DATE OF REVISION OF THE TEXT

25 November 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Update to font styles; editorial changes.
6.4	Update to information regarding use and storage conditions