NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Cuprior 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains trientine tetrahydrochloride equivalent to 150 mg trientine. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, 16 mm x 8 mm oblong film-coated tablet with a score line on each side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cuprior is indicated for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.

4.2. Dose and method of administration

Treatment should only be initiated by specialist physicians with experience in the management of Wilson's disease.

Dose

The starting dose would usually correspond to the lowest dose in the range and the dose should subsequently be adapted according to the patient's clinical response (see section 4.4).

The recommended dose is between 450 mg and 975 mg (3 to 6½ film-coated tablets) per day in 2 to 4 divided doses.

Special populations

Elderly

No dose adjustment is required in elderly patients.

Renal impairment

There is limited information in patients with renal impairment. No specific dose adjustment is required in these patients (see section 4.4).

Paediatric population

The starting dose in paediatrics is lower than for adults and depends on age and body weight.

Children ≥ 5 years

The dose is usually between 225 mg and 600 mg per day (1½ to 4 film-coated tablets) in 2 to 4 divided doses.

Children aged < 5 years

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.

The recommended doses of Cuprior are expressed as mg of trientine base (i.e. not in mg of the trientine tetrahydrochloride salt).

Method of administration

Cuprior is for oral use. The film-coated tablets should be swallowed with water. The scored film-coated tablet can be divided in two equal halves, if required, to provide a more precise dose or facilitate administration.

It is important that Cuprior is 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 medicinal product, food, or milk (see section 4.5).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

When switching a patient from another formulation trientine, caution is advised because doses expressed in trientine base may not be equivalent (see section 4.2).

Trientine is a chelating agent which has been found to reduce serum iron levels. Iron supplements may be necessary in case of iron deficiency anaemia and should be administered at a different time (see section 4.5).

The combination of trientine with zinc is not recommended. There are only limited data on concomitant use available and no specific dose recommendations can be made.

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.

Monitoring

Patients receiving Cuprior should remain under regular medical supervision and be monitored for appropriate control of symptoms and copper levels in order to optimise the dose (see section 4.2).

The aim of maintenance treatment is to maintain free copper levels in the serum within acceptable limits. The most reliable index for monitoring therapy is the determination of serum free copper which is calculated using the difference between the total copper and the ceruloplasmin-bound copper (normal level of free copper in the serum is usually 100 to 150 microgram/L).

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.

Worsening of clinical symptoms, including neurological deterioration, may occur at the beginning of chelation therapy due to excess of free serum copper during the initial response to treatment. Close monitoring is required to optimise the dose or to adapt treatment if necessary.

Special populations

Overtreatment carries the risk of copper deficiency. Monitoring for manifestations of overtreatment should be undertaken, particularly when copper requirements may change, such as in pregnancy (see section 4.6) and in children where appropriate control of copper levels are required to ensure proper growth and mental development.

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).

4.5. Interaction with other medicinal products and other forms of interaction

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 should be taken after at least two hours have elapsed from the administration of trientine.

As trientine is poorly absorbed following oral intake and the principal mechanism of action requires its systemic exposure (see section 5.1), it is important that the film-coated tablets are taken on empty stomach at least one hour before meals or 2 hours after meals and at least one hour apart from any other medicinal product, food, or milk (see section 4.2). This maximises the absorption of trientine and reduces the likelihood of the medicinal product binding to metals in the gastrointestinal tract.

However, no food interaction studies have been performed and so the extent of the food effect on systemic trientine exposure is unknown.

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

Pregnancy

There is a limited amount of data from the use of trientine in pregnant women.

Studies in animals have shown reproductive toxicity, which was probably a result of trientine- induced copper deficiency (see section 5.3).

Cuprior should only be used in pregnancy after careful consideration of the benefits compared with the risks of treatment in the individual patient. Factors which need to be born in mind include the risks associated with the disease itself, the risk of those alternative treatments which are available and the possible teratogenic effects of trientine (see section 5.3).

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

The pregnancy should be closely monitored in order to detect possible foetal 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.

Breast-feeding

It is unknown whether trientine is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Cuprior therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7. Effects on ability to drive and use machines

Cuprior has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction with trientine is nausea. Serious iron deficiency anaemia and severe colitis may occur during treatment.

Tabulated list of adverse reactions

The following adverse reactions have been reported with the use of trientine for Wilson's disease.

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).

System organ class	**Adverse reactions**
Blood and lymphatic system disorders	*Uncommon:* sideroblastic anaemia *Not known:* iron deficiency anaemia.
Gastrointestinal disorders	*Common:* nausea. *Not known:* duodenitis, colitis (including severe colitis).
Skin and subcutaneous tissue disorder	*Uncommon:* skin rash, pruritus, erythema. *Not known*: urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9. Overdose

Occasional cases of trientine overdose have been reported. In cases up to 20 g of trientine base there were no apparent adverse effects reported. A large overdose of 40 g of trientine base which resulted in self-limiting dizziness and vomiting with no other clinical sequelae or significant biochemical abnormalities reported. There is no antidote for trientine acute overdose.

Chronic over treatment can lead to copper deficiency and reversible sideroblastic anaemia. 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).

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

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX12.

Mechanism of action

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.

5.2. Pharmacokinetic properties

Absorption

The absorption of trientine following oral administration is low and variable in patients with Wilson disease. The pharmacokinetic profile of Cuprior has been evaluated after a single oral dose of 450, 600 mg and 750 mg trientine in healthy male and female subjects. Plasma levels of trientine rose rapidly following administration with the median peak level reached after 1.25 to 2 hours. The trientine plasma concentration then declined in a multiphasic manner, initially rapidly, followed by a slower

elimination phase. The overall pharmacokinetic profiles were similar between males and females, although males had higher levels of trientine.

Distribution
Little is known on the distribution of trientine in organs and tissues.

Biotransformation
Trientine is acetylated in two majors metabolites, N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT). MAT may also participate to the overall clinical activity of Cuprior, however the extent of MAT to the overall effect of Cuprior on copper levels remains to be determined.

Elimination
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. Unabsorbed trientine is eliminated through faecal excretion.

Linearity/non-linearity
Plasma exposures in humans have shown a linear relationship with oral doses of trientine.

5.3. Preclinical safety data

Preclinical data obtained with trientine have shown adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use as follows:

Repeat dose toxicity
In mice administered in drinking water, trientine displayed increased frequencies of inflammation of the lung interstitium and liver periportal fatty infiltration. Hematopoietic cell proliferation was seen in the spleen of males. Kidney and body weights were reduced in males as was the incidence of renal cytoplasmic vacuolisation. The NOAEL was established at approximately 92 mg/kg/day for males and 99 mg/kg/day for females. In rats administered oral trientines doses, up to 600 mg/kg/day for 26 weeks, histopathology revealed a dose-related incidence and severity of focal chronic interstitial pneumonitis accompanied by fibrosis of the alveolar wall. The microscopic changes in lung were considered indicative of a persistent inflammatory reaction or persistent toxic effect on alveolar cells. Taking into account that trientine has irritating properties, it was estimated that the observed chronic interstitial pneumonitis was explained by a cytotoxic effect of trientine upon accumulation into bronchiolar epithelial cells and alveolar pneumocytes. These findings were not reversible. The rat NOAEL was considered 50 mg/kg/day for females, a NOAEL was not established for males.

Dogs receiving oral doses of trientine up to 300 mg/kg/day, showed neurological and/or musculo-skeletal clinical symptoms (abnormal gait, ataxia, weak limbs, body tremors) in repeat-dose toxicity studies, attributed to the copper-depleting activity of trientine. The NOAEL was established at 50 mg/kg/day resulting in safety margins of about 4 in males and 17 in females, towards human therapeutic exposures.

Genotoxicity
Overall, 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.

Reproductive and developmental toxicity
When rodents were fed throughout pregnancy a diet containing trientine, the frequency of resorptions and the frequency of abnormal fetuses at term showed a dose-related increase. These effects are possibly due to trientine induced-copper and zinc deficiency.

Local tolerance
In silico data predict that trientine displays irritating and sensitising properties. Positive results for

sensitization potential in Guinea pig maximization tests were reported.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core: Mannitol, Colloidal anhydrous silica, Glycerol dibehenate.

Tablet film-coating: Polyvinyl alcohol, Talc, Titanium dioxyde (E171), Glycerol monocaprylocaprate (Type I), Iron oxide yellow (E172), Sodium laurilsulfate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

OPA/Alu/PVC-Alu blisters, each blister contains 8 film-coated tablets. Pack size: 72 tablets.

6.6. Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Te Arai BioFarma Ltd
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Herne Bay Auckland 1147

0800 TEARAI

9. DATE OF FIRST APPROVAL

25th November 2021

10. DATE OF REVISION OF THE TEXT

25th November 2021