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CUPRIOR (trientine tetrahydrochloride)

▼ 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](http://www.tga.gov.au/reporting-problems).

## AUSTRALIAN PRODUCT INFORMATION – CUPRIOR® (TRIENTINE TETRAHYDROCHLORIDE)

### 1 NAME OF THE MEDICINE

Trientine tetrahydrochloride.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains trientine tetrahydrochloride equivalent to 150 mg trientine.

Trientine tetrahydrochloride is a white powder.

For the full list of excipients, see [Section 6.1 List of excipients](#).

### 3 PHARMACEUTICAL FORM

CUPRIOR (trientine) film-coated 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 halves, each half providing 75 mg trientine.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

CUPRIOR is indicated for the treatment of Wilson's disease in adults, adolescents and children  $\geq 5$  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.

#### Posology

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 Special warnings and precautions for use](#)).

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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 Special warnings and precautions for use](#)).

### 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. The initial dose for children can be expressed on a weight basis as 13 mg/kg/day of trientine base, rounded off to the nearest 75 mg to a maximum of 600 mg, in 2-4 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 Interactions with other medicines and other forms of interactions](#)).

## **4.3 Contraindications**

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

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#### 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 Dose and method of administration](#)).

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 Interactions with other medicines and other forms of interactions](#)).

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 Dose and method of administration](#)).

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 1.6 to 2.4  $\mu\text{mol/L}$ ).

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 Fertility, pregnancy and lactation](#)) and in children

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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 Dose and method of administration](#)).

### **Use in renal impairment**

See Section 4.2 Dose and method of administration.

### **Use in the elderly**

See Section 4.2 Dose and method of administration.

### **Paediatric use**

See Section 4.2 Dose and method of administration.

### **Effects on laboratory tests**

No data 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 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 Pharmacodynamic properties](#)), it is important that the film-coated tablets are taken on an 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 Dose and method of administration](#)). 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.

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## 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

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

Trientine 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.

CUPRIOR should only be used in pregnancy 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 unknown whether trientine is excreted in human milk. A risk to the newborns/infants cannot be excluded. Because many drugs are excreted in human milk, caution should be exercised when trientine tetrahydrochloride is administered to a nursing mother.

## 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 Adverse effects (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.

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#### Tabulated list of adverse events

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

Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

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

#### **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](http://www.tga.gov.au/reporting-problems).

#### **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 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 Special warnings and precautions for use](#)).

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

## 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.

#### Clinical trials

Efficacy was determined through a combination of comparative PK studies (TRIUMPH and TRIUMPH-2, a retrospective survey and published literature reports.

TRIUMPH and TRIUMPH-2 were randomised, double-blind, placebo controlled, cross-over comparative PK studies. A single oral administration of CUPRIOR or trientine dihydrochloride (TETA 2HCL) formulation was administered under fasted conditions and plasma levels of trientine and its two main metabolites were assessed. The results from these studies bridged CUPRIOR to two different trientine formulations (marketed in EU and US) by enabling an oral dose to be recommended that provided the same systemic exposure to existing formulations.

A retrospective survey of the clinical experience of trientine in the management of Wilson's disease has been conducted with two different trientine formulations: a nationally produced tetrachloride (TETA 4HCl) formulation and trientine dihydrochloride (TETA 2HCl). The survey was intended to evaluate the comparability of efficacy and safety of TETA 4HCl and TETA 2HCl. In total, 43 patients with Wilson's disease provided 57 sequences of trientine (TETA) monotherapy of  $\geq 12$  months' duration: 13 sequences with TETA 4HCl and 44 sequences with TETA 2HCl. ) Doses were optimised to the individual patient's needs.

Overall, mean and median serum copper levels and urine copper excretion tended to remain stable or decrease from the beginning to the end of the trientine treatment sequences in both treatment groups. Parameters related to hepatic function, in particular aspartate aminotransferase (AST) and alanine aminotransferase (ALT), improved following both treatments. No notable differences in efficacy were detected when assessing treatment with TETA 4HCl or TETA 2 HCl.

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Long-term efficacy and safety outcomes from a retrospective multicentre cohort study of Wilson's disease patients treated with TETA 2HCl or D-penicillamine was performed by Weiss et al. 2013<sup>1</sup>. Data from chelator-based treatment regimens of over 400 patients was analyzed for their effect on neurologic and hepatic symptoms and for adverse events that led to discontinuation of therapy. Within the study population, 141 patients received trientine. Among those, 103 received trientine as second-line therapy. D-penicillamine and trientine were found to produce comparable outcomes, although D-penicillamine had a higher rate of adverse events.

## 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

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

### Metabolism

Trientine is acetylated into two major metabolites, N<sub>1</sub>-acetyltriethylenetetramine (MAT) and N<sub>1</sub>,N<sub>10</sub>-diacetyltriethylenetetramine (DAT). MAT and DAT are capable of chelating copper, albeit with a lower affinity than trientine. The extent of MAT and DAT to the overall effect of CUPRIOR on copper levels in Wilson's Disease 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. Unabsorbed trientine is eliminated through faecal excretion.

### Linearity/non-linearity

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



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### 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

#### Tablet core:

Mannitol.

Colloidal anhydrous silica.

Glycerol dibehenate.

#### Tablet film-coating:

Polyvinyl alcohol.

Purified talc.

Titanium dioxide.

Polyglycerol esters of fatty acids.

Iron oxide yellow.

Sodium lauryl sulfate.

### 6.2 Incompatibilities

Not applicable.

### 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.

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#### 6.4 Special precautions for storage

Store below 25°C.

#### 6.5 Nature and contents of container

Oriented Polyamide/Aluminium/PVC-Aluminium blisters, each blister contains 8 film-coated tablets.

Pack size: 72 tablets.

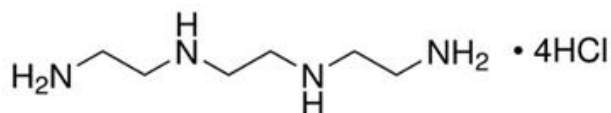
#### 6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

#### 6.7 Physicochemical properties

CUPRIOR contains trientine tetrahydrochloride. The drug substance is a white crystalline powder, freely soluble in water, hydrochloric acid 10% and sodium hydroxide 10%. It is very slightly soluble in methanol and DMSO.

#### Chemical structure



Molecular Formula: C<sub>6</sub>H<sub>22</sub>Cl<sub>4</sub>N<sub>4</sub>

Molecular Weight: 292.08 g.mol<sup>-1</sup> (molecular weight of only trientine is 146.23 g.mol<sup>-1</sup>)

#### CAS number

4961-40-4

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 Prescription Only Medicine

## 8 SPONSOR

JACE Pharma Pty Ltd  
Level 2, 8 Clunies Ross Court  
Brisbane Technology Park  
Eight Mile Plains, Queensland 4113

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## 9 DATE OF FIRST APPROVAL

28/09/2021

## 10 DATE OF REVISION

### Summary table of changes

Section Changed	Summary of new information

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<sup>i</sup> Weiss et al. Efficacy and Safety of Oral Chelators in Treatment of Patients with Wilson Disease, Clinical Gastroenterology and Hepatology 2013; 11:1028-1035