Approval Date：December 29, 2023

Modification Date：February 29, 2024, March 31, 2025, May 29, 2025, July 9th, 2025, July 30, 2025

Package Insert of Trientine Hydrochloride Tablets

Please read this package insert carefully and use the drug under the guidance of your doctor

【Drug Name】

Generic name：盐酸曲恩汀片

English name：Trientine Hydrochloride tablets

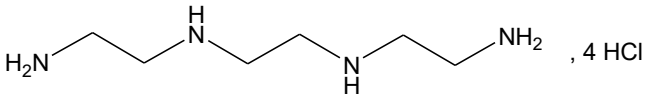
Chinese phonetic alphabet：Yansuan Qu'entingPian

【Ingredients】

The main ingredient of this product is Trientine tetrahydrochloride.

Chemical name ： N'-[2-(2-aminoethylamino)ethyl]ethane-1,2-diamine tetrahydrochloride

Chemical structural formula：



Molecular formula：$C_6H_{22}Cl_4N_4$

Molecular mass：292.08

Excipients

Mannitol，Colloidal silicon dioxide，Glycerol dibehenate, Opadry AMB II Yellow film-coating and purified water. Opadry AMB II Yellow film-coating is composed of Polyvinyl alcohol， Talc， Titanium dioxide (E171)， Glycerol monocaprylocaprate (Type I)，Iron oxide yellow (E172)，Sodium lauryl sulfate

【Characteristic】Yellow capsule-shaped film-coated tablets, white after removing the film coat, scored on both sides.

【Indications】Cuprior is indicated for the treatment of Hepatolenticular Degeneration in children ≥ 5 years and adults intolerant to penicillamine therapy.

【Strength】150mg（by $C_6H_{18}N_4$）

【Posology and Method of Administration】

Treatment should only be initiated by specialist physicians with experience in the management of Hepatolenticular Degeneration.

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.

The scored filmcoated tablet can be divided in two equal halves, if required, to provide a more precise dose or facilitate administration.

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.

Adults:

The recommended dose is between 450 mg and 975 mg (3 to 6.5film-coated tablets) per day in 2 to 4 divided oral doses.

Children ≥ 5 years:

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

The dose is usually between 225 mg and 600 mg per day (1.5 to 4 film-coated tablets) in 2 to 4 divided oral doses.

Special populations

Renal impairment

There is limited information in patients with renal impairment. No specific dose adjustment is required in these patients.

【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. Neurological deterioration may occur at the beginning of treatment.

Tabulated list of adverse reactions

The following adverse reactions have been reported with the use of trientine for Hepatolenticular Degeneration. 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.

The product information of other trientine drug products also indicated the following adverse reaction:

Blood and lymphatic system disorders

Uncommon: anaemia, aplastic anemia

Nervous system disorders

Uncommon: dystonia, tremor.

Not known: dysarthria, muscle rigidity, neurological deterioration.

Immune system disorders

Not known: lupus-like syndrome, lupus nephritis.

【Contraindications】Hypersensitivity to the active substance or to any of the excipients.

【Precautions】

When switching a patient from other formulation trientine, caution is advised because doses expressed in trientine base may not be equivalent.

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.

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 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.

<u>Monitoring</u>

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.

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 from 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 indicator to assess treatment compliance.

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

For patients presenting primarily neurological symptoms who may be at risk for neurological deterioration at the beginning of treatment, it is also recommended that patients presenting neurological symptoms be monitored every 1 to 2 weeks after treatment initiation until the target dose is reached.

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 【Pregnant and Breast Feeding Women】) 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.

Effects on ability to drive and use machines

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

【Pregnant and Breast Feeding Women】

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.

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.

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.

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.

【Paediatric Population】

The information for Children ≥ 5 years see【Posology and Method of Administration】.

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.

【Elderly Population】

There is limited clinical information in patients ≥ 65 years old to determine whether there is a difference in treatment response between elderly and young patients.

In general, elderly patients are advised to choose dosages carefully, usually starting at the lower end of the recommended dose range for adults, due to decreased liver, kidney or heart function and the high frequency of concurrent disease or combined treatment with other medications.

【Interaction with Other Medicinal Products】

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, 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. 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.

【Overdose】

Occasional cases of trientine overdose have been reported. In cases up to 20 g of trientine there were no apparent adverse effects reported. A large overdose of 40 g of trientine resulted in selflimiting 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 serum non-ceruloplasmin bound copper. Close monitoring is required to optimise the dose or to adapt treatment if necessary.

【Clinical Pharmacology】

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.

Pharmacodynamic (PD)

No relevant PD study data are available for reference.

Pharmacokinetic (PK)

Absorption

The bioavailability of trientine following oral administration is low and largely variable in patients with Hepatolenticular Degeneration. The pharmacokinetic profile of Cuprior has been evaluated after a single oral dose of 450mg, 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 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.

Pharmacogenetics

No relevant study data are available for reference.

【Pharmacology and Toxicology】

Pharmacologic

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.

Toxicology

Genetic toxicity

Trientine was positive in the bacterial reverse mutation (Ames) assay, the in vitro unscheduled DNA synthesis assay in rat hepatocytes, and the sister-chromatid exchange assay in Chinese hamster ovary (CHO) cells. Trientine was negative in the HGPRT gene mutation assay in CHO cells and the in vivo mouse micronucleus assay.

Fertility toxicity

Fertility studies have not been conducted with trientine

In embryo-fetal development studies in rats, trientine was administered orally at doses up to approximately 835 mg/kg/day during organogenesis. An increased incidence of resorptions was observed at a dose lower than the maximum recommended dose (1,500 mg/day trientine free base equivalent), based on body surface area. An increased incidence of fetal abnormalities, including hemorrhage and edema, was observed at 2.7 times the maximum recommended dose, based on body surface area. When pregnant rats were treated with trientine and supplemented with copper (concentration of 50 mcg/g in the diet), fetal abnormalities were markedly reduced, indicating that the mechanism of embryo-fetal harm in rats with no copper supplementation was based on copper depletion (primary pharmacology of trientine).

In embryo-fetal development studies in mice, trientine dihydrochloride was administered orally at doses up to approximately 2,000 mg/kg/day during organogenesis. A dose-dependent increase in the incidence of abnormal fetuses occurred at all doses. Fetal abnormalities included hemorrhages and delayed ossification which were observed starting at 500 mg/kg/day, microcephaly and hydrocephaly starting at 1,000 mg/kg/day, and exencephaly at 2,000 mg/kg/day (the doses were 1.1, 2.1, and 4.3 times the maximum recommended dose, respectively, based

on body surface area). The percentage of dams with total resorption was increased at 2,000 mg/kg/day (5.3 times the maximum recommended dose based on body surface area). The mechanism of embryo-fetal harm (e.g. copper depletion) was not determined in this study.

Carcinogenesis

Oral carcinogenicity studies have not been conducted with trientine.

Others

Severe pulmonary toxicity occurred in a 26-week oral toxicity study of trientine dihydrochloride in rats. However, the relevance of this finding to safety risk in patients with Hepatolenticular Degeneration is unknown. Deaths related to pulmonary injury occurred in male rats at 175 and 600 mg/kg/day (1/12 and 3/20 males, respectively). Pulmonary lesions were observed in male rats at 50 mg/kg/day (lower than the maximum recommended dose [1,500 mg/day trientine free base equivalent] based on body surface area).

In female rats, pulmonary lesions occurred at 175 mg/kg/day (lower than the maximum recommended dose based on body surface area). Pulmonary toxicity was dose-dependent in both sexes. The lesions included alveolar fibrosis, bronchiolar hyperplasia/ epithelialization of alveolar wall, focal chronic interstitial pneumonitis, bronchiolar epithelium hypertrophy, alveolar hemorrhage (males only), necrosis/regenerative hyperplasia of terminal bronchioles (males only), and acute interstitial pneumonitis (males only). Most of the pulmonary lesions remained after a 13-week recovery period, and were considered as irreversible (e.g., alveolar fibrosis, bronchiolar hyperplasia/epithelialization of alveolar wall, focal chronic interstitial pneumonitis). Pulmonary toxicity also occurred in a 13-week oral study of trientine dihydrochloride in mice. The effects included interstitial inflammation and alveolar histiocytic infiltration, observed at a dose approximately equal to the maximum recommended dose based on body surface area. The mechanism of pulmonary toxicity was not clearly established as due to copper depletion (primary pharmacology) or due to other drug activity.

Neurological and/or musculoskeletal clinical signs (abnormal “stiff-legged” gait,

limited use of limb, underactivity, body tremors) occurred in a 26-week oral toxicity study of trientine dihydrochloride in dogs at 5.5 times the estimated human exposure at the maximum recommended dose (based on AUC). The mechanism for these clinical signs was not clearly established as due to copper depletion (primary pharmacology) or due to other drug activity. Because of the severity of the clinical signs at exposures above 5.5 times the maximum exposure in humans, some dogs were sacrificed for humane reasons after 9 weeks of treatment, and treatment for the remaining animals in the same dose group was stopped after 10 weeks. Neurological and/or musculoskeletal clinical signs were generally not observed at exposures that were 3.4 times the human exposure at the maximum recommended dose.

【Storage】Not more than 25ºC, sealed storage

【Package】

Oriented polyamine/aluminum/polyvinyl chloride cold form blister and pharmaceutical aluminum foil packaging, each blister contains 8 film-coated tablets, each carton contains 9 blisters or 12 blisters.

【Shelf Life】36 months.

【Executive Standard】JX20230144

【Approval Number】国药准字 HJ20230149

【Marketing Authorization Holder】

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