Trientine 250 MG

Hydrochloride Capsules USP

TAJ PHARMA

TRIENTINE- trientine hydrochloride capsules

TRIENTINE (trientine hydrochloride) Capsules
Rx only

DESCRIPTION

Trientine hydrochloride is *N,N'*-bis (2-aminoethyl)-1,2-ethanediamine dihydrochloride. It is a white to pale yellow crystalline hygroscopic powder. It is freely soluble in water, soluble in methanol, slightly soluble in ethanol, and insoluble in chloroform and ether. The empirical formula is C H N •2HCl with a molecular weight of 219.2. The structural formula is:

NH (CH) NH(CH) NH(CH) NH •2HCl

Trientine hydrochloride is a chelating compound for removal of excess copper from the body. TRIENTINE (trientine hydrochloride) is available as 250 mg capsules for oral administration. TRIENTINE capsules contain gelatin, iron oxides, stearic acid, and titanium dioxide as inactive ingredients.

CLINICAL PHARMACOLOGY

Introduction

Wilson's disease (hepatolenticular degeneration) is an autosomal inherited metabolic defect resulting in an inability to maintain a near-zero balance of copper. Excess copper accumulates possibly because the liver lacks the mechanism to excrete free copper into the bile. Hepatocytes store excess copper but when their capacity is exceeded copper is released into the blood and is taken up into extrahepatic sites. This condition is treated with a low copper diet and the use of chelating agents that bind copper to facilitate its excretion from the body.

Clinical Summary

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 hydrochloride. 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 hydrochloride 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 hydrochloride experienced a recurrence of the symptoms of systemic lupus erythematosus which had appeared originally during therapy with penicillamine. Therapy with trientine hydrochloride was discontinued. No other adverse reactions, except iron deficiency, were noted among any of these 41 patients.

One investigator treated 13 patients with trientine hydrochloride following their development of intolerance to d-penicillamine. Retrospectively, he 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 hydrochloride group received d-penicillamine for an average of 4 years as compared to an average of 10 years for the non- ® 6 18 4

2 2 2 2 2 2 2 2

treated group.

Various laboratory parameters showed changes in favor of the patients treated with trientine hydrochloride. 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 hydrochloride. In the 13 patients treated with trientine hydrochloride, 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 hydrochloride 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 hydrochloride treatment.

The clinical outcome of the two groups also differed markedly. Of the 13 patients on therapy with trientine hydrochloride (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 hydrochloride has cupriuretic activities in both normal and copper-loaded rats. In general, the effects of trientine hydrochloride on urinary copper excretion are similar to those of equimolar doses of penicillamine, although in one study they were significantly smaller.

Human Studies

Renal clearance studies were carried out with penicillamine and trientine hydrochloride 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 hydrochloride. The mean urinary excretion rates of copper were as follows:

No. of Patients
Single Dos e Treatment Bas al Excretion Rate (µg Cu + + /6hr)
Tes t-dos e 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 Dos e Treatment Bas al Excretion Rate (µg Cu + + /6hr)
Tes t-dos e Excretion Rate (µg Cu + + /6hr)
8 Trientine, 1.2 g 71 1326
7 Penicillamine, 500 mg 68 1074

These results demonstrate that TRIENTINE 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.

Pharmacokinetics

Data on the pharmacokinetics of trientine hydrochloride are not available. Dosage adjustment recommendations are based upon clinical use of the drug (see DOSAGE AND ADMINISTRATION). **INDICATIONS AND USAGE**

TRIENTINE is indicated in the treatment of patients with Wilson's disease who are intolerant of penicillamine. Clinical experience with TRIENTINE is limited and alternate dosing regimens have not been well-characterized; all endpoints in determining an individual patient's dose have not been well defined.

TRIENTINE and penicillamine cannot be considered interchangeable. TRIENTINE should be used when continued treatment with penicillamine is no longer possible because of intolerable or life endangering side effects.

Unlike penicillamine, TRIENTINE is not recommended in cystinuria or rheumatoid arthritis. The absence of a sulfhydryl moiety renders it incapable of binding cystine and, therefore, it is of no use in cystinuria. In 15 patients with rheumatoid arthritis, TRIENTINE was reported not to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment.

TRIENTINE is not indicated for treatment of biliary cirrhosis.

CONTRAINDICATIONS

Hypersensitivity to this product.

WARNINGS

Patient experience with trientine hydrochloride is limited (see CLINICAL PHARMACOLOGY).

Patients receiving TRIENTINE should remain under regular medical supervision throughout the period of drug administration. Patients (especially women) should be closely monitored for evidence of iron deficiency anemia.

PRECAUTIONS

General

There are no reports of hypersensitivity in patients who have been administered trientine hydrochloride for Wilson's disease. However, there have been reports of asthma, bronchitis and dermatitis occurring after prolonged environmental exposure in workers who use trientine hydrochloride as a hardener of epoxy resins. Patients should be observed closely for signs of possible hypersensitivity.

Information for Patients

Patients should be directed to take TRIENTINE 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. The capsules should be swallowed whole with water and should not be opened or chewed. Because of the potential for contact dermatitis, any site of exposure to the capsule contents should be washed with water promptly. For the first month of treatment, the patient should have his temperature taken nightly, and he should be asked to report any symptom such as fever or skin eruption.

Laboratory Tests

The most reliable index for monitoring treatment is the determination of free copper in the serum, which equals the difference between quantitatively determined total copper and ceruloplasmin-copper. Adequately treated patients will usually have less than 10 mcg free copper/dL of serum.

Therapy may be monitored with a 24-hour urinary copper analysis periodically (i.e., every 6-12 months). Urine must be collected in copper-free glassware. Since a low copper diet should keep copper absorption down to less than one milligram a day, the patient probably will be in the desired state of negative copper balance if 0.5 to 1.0 milligram of copper is present in a 24-hour collection of urine.

Drug Interactions

In general, mineral supplements should not be given since they may block the absorption of TRIENTINE. 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 each inhibit absorption of the other, two hours should elapse between administration of TRIENTINE and iron. It is important that TRIENTINE 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Data on carcinogenesis, mutagenesis, and impairment of fertility are not available.

Pregnancy

Trientine hydrochloride was teratogenic in rats at doses similar to the human dose. The frequencies of both resorptions and fetal abnormalities, including hemorrhage and edema, increased while fetal copper levels decreased when trientine hydrochloride was given in the maternal diets of rats. There are no adequate and well-controlled studies in pregnant women. TRIENTINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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 is administered to a nursing mother.

Pediatric Use

Controlled studies of the safety and effectiveness of TRIENTINE in pediatric patients have not been conducted. It has been used clinically in pediatric patients as young as 6 years with no reported adverse experiences.

Geriatric Use

Clinical studies of TRIENTINE 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.

ADVERSE REACTIONS

Clinical experience with TRIENTINE has been limited. The following adverse reactions have been reported in a clinical study in patients with Wilson's disease who were on therapy with trientine hydrochloride: iron deficiency, systemic lupus erythematosus (see CLINICAL PHARMACOLOGY). In addition, the following adverse reactions have been reported in marketed use: dystonia, muscular spasm, myasthenia gravis.

TRIENTINE is not indicated for treatment of biliary cirrhosis, but in one study of 4 patients treated with trientine hydrochloride for primary biliary cirrhosis, the following adverse reactions were reported: heartburn; epigastric pain and tenderness; thickening, fissuring and flaking of the skin; hypochromic microcytic anemia; acute gastritis; aphthoid ulcers; abdominal pain; melena; anorexia; malaise; cramps; muscle pain; weakness; rhabdomyolysis. A causal relationship of these reactions to drug therapy could not be rejected or established.

Store protected from moisture at a temperature not exceeding 2°C to 8°C (Cold Storage).

Pack size: is 10,30,50,100,120 & 500 Capsules.

MFG. IN INDIA BY:
TAJ PHARMACEUTICALS LTD.
at : Tal - Sanand ,Dist. Ahmedabad,
Gujarat (India)
MFG. LIC.No. : xxxxxxxxxxx

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in May 2018.

Trientine 250 MG
Hydrochloride Capsules USP