TRIENTINE HYDROCHLORIDE- trientine hydrochloride capsule
Kadmon Pharmaceuticals, LLC

Trientine Hydrochloride Capsules, USP

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 $C_6H_{18}N_4 \cdot 2HCl$ with a molecular weight of 219.2. The structural formula is:

$NH_2(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2 \cdot 2HCl$

Trientine hydrochloride is a chelating compound for removal of excess copper from the body. Trientine Hydrochloride Capsules, USP are available as 250 mg capsules for oral administration. Each capsule contains 250 mg trientine hydrochloride, USP and the inactive ingredient stearic acid. The capsule shell consists of gelatin and titanium dioxide. The capsule shell ink contains shellac, titanium dioxide, FD&C yellow #5 aluminum lake, FD&C blue #1 aluminum lake, FD&C blue#2/indigo carmine aluminum lake, and FD&C blue #1/brilliant blue FCF aluminum lake.

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-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 Dose Treatment	Basal Excretion Rate (mcg Cu + + /6hr)	Test-dose Excretion Rate (mcg 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 (mcg Cu + + /6hr)	Test-dose Excretion Rate (mcg Cu + + /6hr)
8	Trientine, 1.2 g	71	1326
7	Penicillamine, 500 mg	68	1074

These results demonstrate that Trientine hydrochloride 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 hydrochloride is indicated in the treatment of patients with Wilson's disease who are intolerant of penicillamine. Clinical experience with Trientine hydrochloride 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 hydrochloride and penicillamine cannot be considered interchangeable. Trientine hydrochloride should be used when continued treatment with penicillamine is no longer possible because of intolerable or life endangering side effects.

Unlike penicillamine, trientine hydrochloride 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 hydrochloride was reported not to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment.

Trientine hydrochloride 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 hydrochloride 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.

This product contains FD&C Yellow #5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow #5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Information for Patients

Patients should be directed to take trientine hydrochloride 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 hydrochloride. 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 hydrochloride each inhibit absorption of the other, two hours should elapse between administration of trientine hydrochloride and iron.

It is important that trientine hydrochloride 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 hydrochloride 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 hydrochloride is administered to a nursing mother.

Pediatric Use

Controlled studies of the safety and effectiveness of trientine hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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.

To report SUSPECTED ADVERSE REACTIONS, contact Kadmon Pharmaceuticals, LLC at 1-877-377-7862 or FDA at 1-800-FDA-1088 or

www.fda.gov/medwatch.

OVERDOSAGE

There is a report of an adult woman who ingested 30 grams of trientine hydrochloride without apparent ill effects. No other data on overdosage are available.

DOSAGE AND ADMINISTRATION

Systemic evaluation of dose and/or interval between dose has not been done. However, on limited clinical experience, the recommended initial dose of trientine hydrochloride is 500-750 mg/day for pediatric patients and 750-1250 mg/day for adults given in divided doses two, three or four times daily. This may be increased to a maximum of 2000 mg/day for adults or 1500 mg/day for pediatric patients age 12 or under.

The daily dose of trientine hydrochloride 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 6-12 month intervals (see **PRECAUTIONS, Laboratory Tests**).

It is important that trientine hydrochloride 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 drug, food, or milk. The capsules should be swallowed whole with water and should not be opened or chewed.

HOW SUPPLIED

Trientine Hydrochloride Capsules, USP, 250 mg are opaque white capsules coded KD034 250 mg on the body of the capsule printed in green ink and Kadmon ® on the cap of the capsule printed in blue ink. They are supplied as follows:

NDC 66435-700-10 in bottles of 100.

NDC 66435-700-12 blister pack (contains 12 Clovique (trientine hydrochloride), capsules 250mg).

NDC 66435-700-20 carton (contains 10 Clovique blister packs)

STORAGE

Bottle:

Keep container tightly closed.

Store at 2-8°C (36°F and 46°F).

Carton/Blister Pack:

Clovique carton should be kept refrigerated at 2-8°C (36°F and 46°F).

For patient convenience, individual blister pack (or tray) may be stored for a maximum single period of 30 days at or below room temperature (25°C (77°F)) with protection from sources of heat and humidity. Capsules stored at room temperature should be discarded after 30 days.

Manufactured by:
Xcelience
Tampa, FL 33607, USA

Manufactured For:
Kadmon Pharmaceuticals, LLC
Warrendale, PA 15086, USA

C151.00042

Rev. 12/2018

PRINCIPAL DISPLAY PANEL - Bottle Label

NDC 66435-700-10 Rx only

Trientine Hydrochloride

Capsules, USP

250 mg

Each capsule contains

trientine hydrochloride 250 mg

Kadmon ®

Pharmaceuticals, LLC 100 capsules

Store at 2-8°C (36-46°F).

Usual Dosage: See accompanying

prescribing information.

Keep container tightly closed.

Dispense in tight container.

Contains FD&C Yellow No. 5

(tartrazine) as a color additive.

Distributed by:

Kadmon Pharmaceuticals, LLC

Warrendale, PA 15086, USA

Manufactured by:

Xcelience

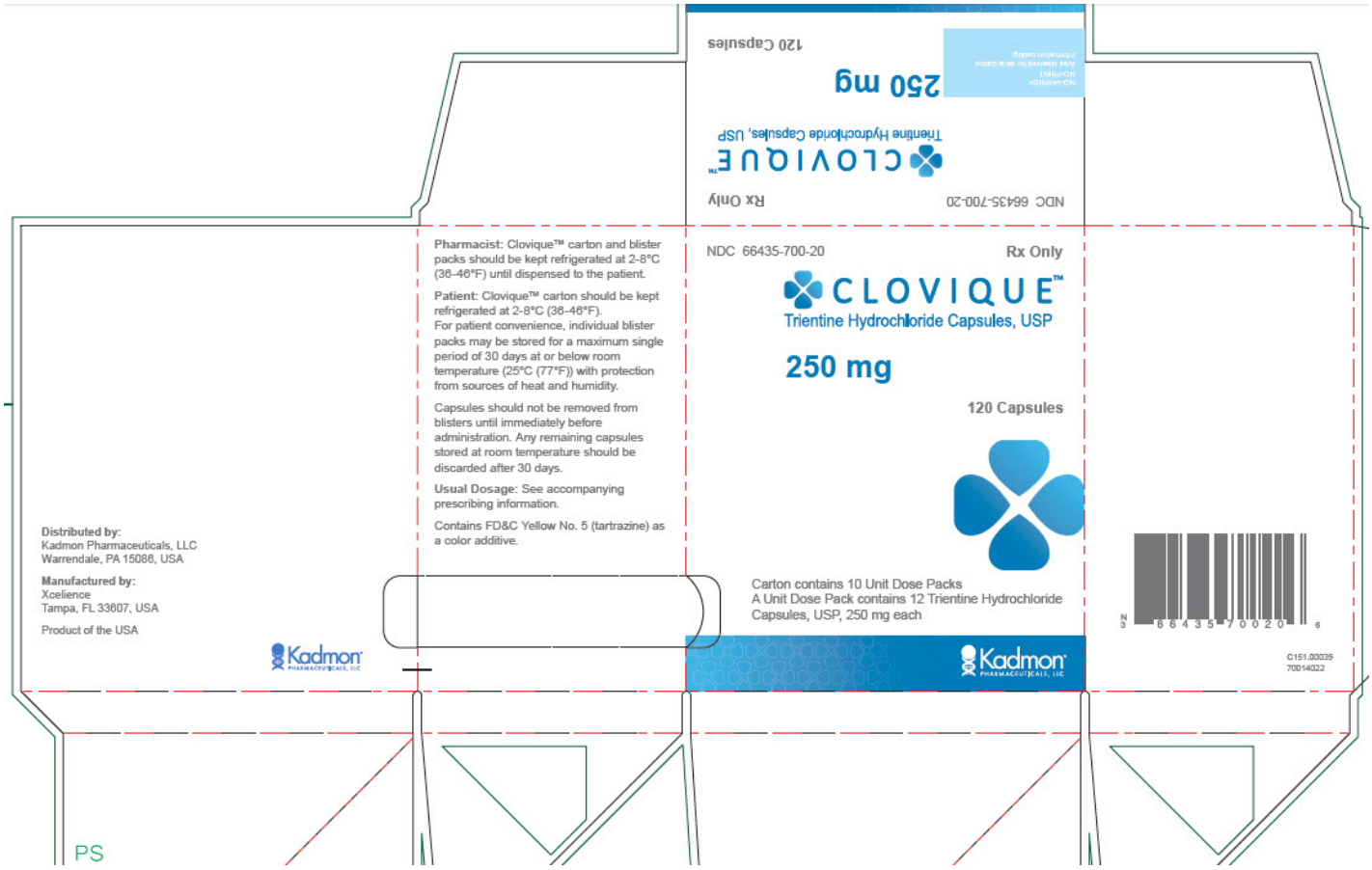
Tampa, FL 33607, USA

Product of the USA

C151.00038

70014020

PRINCIPAL DISPLAY PANEL - Blister Carton



NDC 66435-700-20 Rx Only

CLOVIQUE™
Trientine Hydrochloride Capsules, USP

250 mg

120 Capsules

Carton contains 10 Unit Dose Packs
A Unit Dose Pack contains 12 Trientine Hydrochloride Capsules, USP, 250 mg each

Kadmon®
Pharmaceuticals, LLC

Pharmacist: Clovique™ carton and blister packs should be kept refrigerated at 2-8°C (36-46°F) until dispensed to the patient.

Patient: Clovique™ carton should be kept refrigerated at 2-8°C (36-46°F).
For patient convenience, individual blister packs may be stored for a maximum single period of 30 days at or below room temperature (25°C (77°F)) with protection from sources of heat and humidity.

Capsules should not be removed from blisters until immediately before administration. Any remaining capsules stored at room temperature should be discarded after 30 days.

Usual Dosage: See accompanying prescribing information.

Contains FD&C Yellow No. 5 (tartrazine) as a color additive.

Distributed by:
Kadmon Pharmaceuticals, LLC
Warrendale, PA 15086, USA

Manufactured by:
Xcelience
Tampa, FL 33607, USA

Product of the USA

C151.00039
70014022

TRIENTINE HYDROCHLORIDE

trientine hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66435-700
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TRIENTINE HYDROCHLORIDE (UNII: HC3NX54582) (TRIENTINE - UNII:SJ76Y07H5F)	TRIENTINE HYDROCHLORIDE	250 mg

Inactive Ingredients

Ingredient Name	Strength
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FD&C YELLOW NO. 5 (UNII: I753WB2F1M)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	white (opaque)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	KD034;250mg;Kadmon
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66435-700-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/30/2019	09/30/2021
2	NDC:66435-700-12	12 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/21/2019	09/30/2021
3	NDC:66435-700-20	10 in 1 CARTON; Type 0: Not a Combination Product	10/21/2019	09/30/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209415	09/30/2019	09/30/2021

Labeler - Kadmon Pharmaceuticals, LLC (843913216)

Revised: 4/2021

Kadmon Pharmaceuticals, LLC