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NDA

19194

AP LTR

87
NDA 19-194

Merck Sharp & Dohme Research Laboratories
 Division of Merck & Co., Inc.
 Attention: Gerard D. Picot, Ph.D.
 West Point, PA 19406

Dear Dr. Picot:

Please refer to your December 30, 1983 new drug application, submitted on February 20, 1985 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cuprid (trientina hydrochloride) Capsules.

We also acknowledge receipt of your amendments dated September 9, and October 24, 1985 and are pleased to see your commitment to pursue studies directed toward clarification of the relative potency of Cuprid and its dependence of its effectiveness on cupuresis.

We have completed the review of this application including the submitted draft labeling and the application is approved effective on the date of this letter. Prior to marketing, however, please submit twelve copies of the final printed labeling identical in content to the enclosed draft. Marketing of the drug before the changes specified are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

Please mount seven copies of the labeling individually on heavy weight paper or similar material.

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed - but is ongoing in our laboratories. In such a case the policy of the Center for Drugs and Biologics is to proceed with approval.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Ms. Cathy Neid
 Consumer Safety Officer
 Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
 Director
 Office of Drug Research and Review
 Center for Drugs and Biologics

NDA

19/94

AE LTR

NEA 19-194

AUG 30 1985

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
Attention: Gerard D. Picot, Ph.D.
West Point, PA 19466

Dear Dr. Picot:

Please refer to your December 28, 1982 new drug application resubmitted on February 20, 1985 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cuprid (trientine hydrochloride) Capsules.

We also acknowledge receipt of your amendments dated July 11, October 2 and October 11, 1984; January 29 (two), February 5, February 12, February 20, February 28, April 18, May 29, June 5, July 3, July 24, and August 23, 1985.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit another draft of the labeling as outlined below and as indicated on the enclosed marked up draft labeling.

Note that the established name for Cuprid is trientine hydrochloride, not dihydrochloride; this name should be used in all labeling. In addition, the labeling starting on page 2 (Clinical Pharmacology) through page 3 of the same section should conform to the following outline:

- 1) The first paragraph of the new labeling should be the second paragraph of the current labeling.
- 2) The second paragraph should summarize the findings that are in fact the basis for approval of Cuprid, viz, that patients who have received Cuprid in place of penicillamine have a significantly different time course of relapse than patients who have had penicillamine discontinued and have not received Cuprid. The number of patients and the duration of treatment should be specified.
- 3) The third paragraph should describe the chelating properties of Cuprid compared to penicillamine and the potency comparison of Cuprid and penicillamine on cupruresis in copper loaded rodents.
- 4) The fourth paragraph should contain information on the pharmacokinetics of Cuprid and data that lead to the dosing recommendations.
- 5) The fifth paragraph should be the fourth paragraph of the current labeling.
- 6) The sixth paragraph should indicate the basis used for dosage titration.
- 7) The seventh paragraph should be the third paragraph of the current labeling.

Please also modify the Dosage and Administration section to include the monitoring suggestions provided in the Draft Summary Basis of Approval submitted on August 23, 1985.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

We have communicated to you our concern that equieffective doses of Cuprid and penicillamine have not been identified. Indeed, the current recommended doses may well be too low. Although the recommended doses may materially slow the progression of disease, they may be too small to prevent progression as effectively as penicillamine. You are also aware of our concern that suitable instructions for adjusting the dose of Cuprid have not been developed.

Final approval of Cuprid will be based on our understanding that you are committed to determining:

- a) The relative potency of Cuprid and penicillamine for cupruresis in patients with Wilson's disease.
- b) Whether or not the beneficial effect of Cuprid is dependent upon cupruresis or some other means of depleting total body stores of copper.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second copy, with a copy of the package insert, directly to the Director, Division of Drug Advertising and Labeling (HFN-240). Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Cathy Heald
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:

Original NDA

HFII-110

HFN-240 (with draft labeling)

HFN-83

HF-35/RGregorio

HFN-100/Dr. Temple

HFN-110/Cheald/7/03/85;7/10/85;8/27/85

cb/7/10/85;sb/8/6/85;8/27/85;8/27/85/0396v ..

R/D: MBachrach/7/23/85;8/27/85

RWolters/7/24/85;8/27/85

JWilliams/7/24/85

CResnack/7/24/85;8/27/85

MMorgenstern/8/5/85;8/27/85

RLipicky/8/24/85

RKeenan/8/27/85

APPROVABLE

NDA

19-194

FPL

CAPSULES

MSD | **CUPRID®**
 (TRIENTINE HYDROCHLORIDE, MSD)

CUPRID®
 (Trientine Hydrochloride, MSD)

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 $C_6H_{16}N_4 \cdot 2HCl$ with a molecular weight of 219.2. The structural formula is:



Trientine hydrochloride is a chelating compound for removal of excess copper from the body. CUPRID® (Trientine Hydrochloride, MSD) is available as 250 mg capsules for oral administration. Capsules CUPRID contain stearic acid as an inactive ingredient.

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

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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 there 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

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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 (µg Cu ⁺⁺ /6hr)	Test-dose Excretion Rate (µg Cu ⁺⁺ /6hr)
6	Trientine 1.2 g	19	134
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 (µg Cu ⁺⁺ /6hr)	Test-dose Excretion Rate (µg Cu ⁺⁺ /6hr)
8	Trientine 1.2 g	71	1324
7	Penicillamine 500 mg	88	1074

These results demonstrate that CUPRID 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

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

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

CUPRID is not indicated for treatment of biliary cirrhosis.

CONTRAINDICATIONS

Hypersensitivity to this product.

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WARNINGS

Patient experience with trientine hydrochloride is limited (see CLINICAL PHARMACOLOGY). Patients receiving CUPRID 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 CUPRID 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 CUPRID. 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 CUPRID each inhibit absorption of the other, two hours should elapse between administration of CUPRID and iron.

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It is important that CUPRID 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

Pregnancy Category C. 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. CUPRID 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 CUPRID is administered to a nursing mother.

Pediatric Use

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

ADVERSE REACTIONS

Clinical experience with CUPRID has been limited. The following adverse reactions have been reported in patients with Wilson's disease who were on therapy with trientine hydrochloride: iron deficiency, systemic lupus erythematosus (see CLINICAL PHARMACOLOGY).

CUPRID 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.

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suring 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.

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 CUPRID is 500 - 750 mg/day for children 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 children age 12 or under. The daily dose of CUPRID 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 CUPRID 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

No. 3511 — Capsules CUPRID, 250 mg, are light brown opaque capsules and are coded MSC 679. They are supplied as follows:

NLC 0006-0679-68 in bottles of 100.

Storage

Keep container tightly closed.

Store at 2° - 8°C (35.6° - 46.4°F).

MSD MERCK SHARP & DOHME
DIV. OF MERCK & CO., INC., WEST POINT, PA. 19380, USA

NDA

19194

SBA

Wolter

Summary Basis of Approval

NDA 19-194

Drug Generic Name:
Trientine Hydrochloride

Applicant:
Merck Sharp & Dohme
Research Laboratories
Sumneytown Pike
West Point, PA 19486

Drug Trade Name:
Cuprid

I. Indications for Use:

CUPRID is indicated in the treatment of patients with Wilson's disease who are intolerant to penicillamine.

II. Dosage form, route of administration and recommended dosage:

Cuprid is a capsule that contains 250 mg of trientine hydrochloride. Systematic evaluation of dose and/or interval between doses has not been done. Based on limited clinical experience, however, the recommended initial dose of Cuprid is 500-750 mg/day for children and 750-1250 mg/day for adults given in divided doses two, three, or four times daily. The daily dose of Cuprid should be increased to a maximum of 2400 mg/day for adults or 1500 mg/day for children (age 12 and under) if clinical response is not satisfactory or if urinary and/or serum copper levels are persistently and significantly high. Optimal long-term maintenance dosage should be determined by urinary and/or serum copper analysis.

It is important that Cuprid 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.

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. A physical examination, white count, platelet count, hemoglobin, and routine urinalysis should be completed as clinically indicated. Determinations of SGOT, SGPT, serum bilirubin, and free serum copper should also be made. The dosage of Cuprid must be decreased if liver functions deteriorate or if free serum copper increases. The dosage should be reduced or the drug withdrawn if a low serum iron or iron-deficiency anemia develops, particularly if no response to oral iron therapy occurs.

III. Manufacturing and Control:

A. Manufacturing and Controls

Bulk trientine HCl is supplied to Merck Sharp & Dohme by Eastman Kodak (DMF 5351) and Aldrich Chemical Company (DMF 1796). Satisfactory letters of authorization have been submitted to the Agency allowing Merck to reference these Drug Master Files for a description of the synthesis. Bulk chemical controls proposed for the new drug substance are adequate to demonstrate its suitability for use.

The manufacturing and control procedures for the CUPRID capsules are adequately discussed and are sufficient to characterize the product and assure its identity, strength, quality, and purity.

B. Stability

Stability data are provided which support an 18-month expiration date when the capsules are stored under refrigeration (2-8°C). Because of the limited availability and use of this product, Merck may retest product stored under its control after a one year period to extend the expiration date.

C. Methods Validation

The required analytical methods for trientine hydrochloride and for CUPRID capsules is ongoing in our laboratories. In such a case the policy of the Center for Drugs and Biologics is to proceed with approval.

D. Labeling

Labeling components, including the immediate container and carton labels for bulk capsules in bottles, and the package insert, are in full compliance with technical requirements for proprietary name, non-proprietary name, ingredient statement, control number, expiration date, prescription caution, applicant's name and address, storage statement, net contents, and contain all specific requirements as provided for in 21 CFR 201 subparts A and B. The tradename, CUPRID, is not in conflict with a name of any other drug.

E. Establishment Inspection

The applicant's operations at the relevant facilities have been found to be in compliance with CGMP regulations as verified by the Manufacturing Review Branch (MFN-322).

F. Environmental Impact Analysis Report

The applicant provided information in the December 30, 1983 submission that indicates the production and use of the product will have no adverse effect on the environment. The disposal of wastes generated in the manufacturing facilities is controlled in accordance with appropriate local, state, and federal regulations.

Further environmental considerations are not necessary with the approval of this application.

IV. Pharmacology:

A. Copper Chelating Activity

Studies in vitro demonstrate that trientine hydrochloride is an effective chelator of serum copper. Jackson et al⁽⁴⁾, showed that it effectively chelated protein-bound copper from solutions of human serum, plasma, and pure ceruloplasmin. Each solution was treated with trientine hydrochloride and other chelating agents, and the resulting low molecular weight species were separated by ultrafiltration. Copper concentrations in each fraction were then determined by atomic absorption spectrophotometry. The effect of trientine hydrochloride was time- and concentration-dependent, and increased markedly above $10^{-2}M$. May and Williams⁽⁵⁾ in another report predicted from computer models that trientine hydrochloride begins to mobilize copper at concentrations as low as $10^{-9}M$ in humans.

Studies in animals have shown that trientine hydrochloride has cupriuretic activities in both normal and copper-loaded rats. Planas-Bohne⁽⁶⁾ loaded Sprague-Dawley rats (average starting weight 105 g) with 189 mg of cupric ion (Cu^{++}) over a 20-day period. The rats were then treated I.P. for 5 days with a chelating agent (50 $\mu mol/kg$) or saline control. Daily urinary copper excretion was measured after discontinuation of copper loading with the following results:

<u>Chelator</u>	<u>Dose</u>	<u>Urinary Cu Excretion</u> <u>(μg Cu/24 hr)</u>
Trientine	11 mg/kg	15.44 $\pm$ 0.53*
Penicillamine	7.5 mg/kg	26.26 $\pm$ 1.55*
Dimercaptopropane sulfonate (DMPS)	9.4 mg/kg	24.64 $\pm$ 0.95*
Control (saline)	---	10.02 $\pm$ 0.99

*Significantly different from control, p less than 0.01.

As illustrated in the table, trientine hydrochloride had a significant effect on urinary copper excretion relative to the control, but was less potent than penicillamine.

Daily copper excretion increased as a function of increasing the dose from 25 $\mu\text{mol/kg}$ to 50 $\mu\text{mol/kg}$ for trientine hydrochloride and penicillamine. Doses of 100 $\mu\text{mol/kg}$ of each drug produced a greater but less than expected copper output over that seen at the 50 $\mu\text{mol/kg}$ dose.

Gibbs and Walshe⁽³⁾ compared the cupriuretic effects of trientine hydrochloride and other tetramines and penicillamine in rats. The compounds were given by mouth as a standard dose of 100 mg. The urinary excretion of copper was determined by atomic absorption spectrophotometry. The daily basal urine copper excretion by the rat was $65.1 \pm \text{S.E. } 2.93 \text{ nmol/24 hours}$ ($4.1 \mu\text{g} \pm 0.185$). After penicillamine this rose to $367.1 \text{ nmol/24 hrs}$ ($23.3 \mu\text{g}$) and after trientine dihydrochloride to $305.9 \text{ nmol/24 hrs}$ ($19.4 \mu\text{g}$).

Borthwick et al⁽¹⁾ compared the cupriuretic effects of trientine hydrochloride and other tetramines and d-penicillamine in normal and copper-loaded rats. Compared to a one-day control period, penicillamine and trientine hydrochloride (4 $\mu\text{mol/100 gm}$ body weight daily for 2 days) induced significant (p less than 0.01) cupriuresis in both the normal and copper-loaded rats. Although the mean response to penicillamine was greater than with trientine hydrochloride, the difference between the two agents was not statistically significant. Renal clearance studies in normal rats after intravenous administration of penicillamine, trientine hydrochloride, and 2,3,2,-tetramine showed that trientine hydrochloride was slightly more effective than penicillamine. During infusion, the renal clearance of copper was 96.2 ul/min following 2,3,2-tetramine administration, 66.2 ul/min after trientine dihydrochloride and 41.2 ul/min after penicillamine.

B. Toxicologic Evaluation

In a study performed by the National Center for Toxicological Research (NCTR), male and female mice (B6C3F1) were given 0, 120, or 3000 ppm trientine hydrochloride in their drinking water and fed either AIN-76A or NIH-31 diets for 90 days. An additional control group was fed a copper deficient AIN-76A

diet. On a body weight basis trientine dosage was estimated (from average weekly body weight and water consumption data) as follows:

Diet	Concentration in Water (ppm)	Daily Trientine Dosage (mg/kg)	
		Females	Males
AIN-76	120	19.4	17.2
AIN-76	600	98.4	91.8
AIN-76	3000	498	447
NIH-31	120	22.3	22.0
NIH-31	600	109.2	109.2
NIH-31	3000	558	498

The highest dosage level of trientine hydrochloride was associated with a depression of weight gain in males on the AIN-76A (19%) or NIH-31 (9%) diets. Males and females on the copper deficient diet gained more than controls fed an unaltered diet. The high dose level was also associated with depression of kidney weights and a decreased incidence of renal tubule vacuolization in males fed the AIN-76A diet. Chronic fibrosing interstitial pneumonia developed in both male (14/20) and female (18/20) mice receiving 3000 ppm trientine and the AIN-76A diet. This lesion did not occur in AIN-76A controls, lower dose groups, copper deficient controls or in NIH-31 diet groups.

In another study performed by the NCTR, male and female rats (Fisher 344) were given 0, 120, 600 or 3000 ppm trientine hydrochloride in their drinking water and fed either AIN-76A or NIH-31 diets for 90 days. As in the mouse study described above, an additional control group was fed a copper deficient AIN-76A diet. On a body weight basis, trientine dosage was estimated (from average weekly body weight and water consumption data) as follows:

Diet	Concentration in Water (ppm)	Daily Trientine Dosage (mg/kg)	
		Females	Males
AIN-76	120	12.6	9.8
AIN-76	600	58.2	49.3
AIN-76	3000	312	246
NIH-31	120	13.8	9.4
NIH-31	600	67.8	49.6
NIH-31	3000	336	243

With either diet, trientine hydrochloride administration (all dose levels) was associated with greater frequency and/or severity of uterine dilatation. In the high dose animals receiving the AIN-76A diet, the incidence of uterine dilatation clearly exceeded that of the copper deficient control group. A decreased prevalence of uterine epithelial necrosis in copper deficient animals suggested that trientine hydrochloride treated animals exhibiting uterine dilatation were responding to estrus suppression induced by a marginal copper deficiency. The most notable findings associated with the copper deficient diet were diffuse atrophy, multifocal necrosis and chronic inflammation of the pancreas (the latter effect was primarily limited to males). Also occurring in animals fed the copper deficient diet and absent in control was hematopoietic cell proliferation of the spleen.

Information relevant to a teratogenic potential for trientine hydrochloride has been published as a letter to the editor of Lancet (Keen et al, Lancet No. 8281, Vol.I, May 15, 1982, p. 1127) and as an abstract in Federation Proceedings (Cohen et al, Fed.Proc.41:944, 1982). Sprague Dawley rats were fed a complete purified control diet (containing 5 ppm copper) or the same diet with trientine hydrochloride added at levels of 0.17, 0.83, or 2.66% throughout pregnancy. Trientine hydrochloride levels were said to be comparable to those used clinically. At term, day 21 of pregnancy, fetuses were removed and examined for visible malformations, and maternal tissues and fetuses were analyzed. Other than a lower than normal weight gain in dams of the intermediate and high dosage groups (food intake similar in all groups), pregnant rats appeared healthy throughout the experiment. Fetal outcome, however, was very different among groups. Frequencies of both resorptions and fetal anomalies (primarily massive hemorrhaging and edema) were dose-related. Trientine hydrochloride also had a pronounced effect on tissue copper and zinc concentrations. Maternal plasma copper concentrations decreased with increasing trientine hydrochloride exposure. Copper concentration in fetal liver was similarly affected. Concentration of zinc in fetal liver, in contrast to copper, increased with increasing trientine exposure. A similar effect on zinc was observed in maternal kidneys (data relevant to the latter observation not supplied).

Trientine HCl in Diet	(n)	Maternal Plasma Copper (mcg/dl)	Resorp tions	Abnormal Fetuses	Fetal Liver Conc. Cu (mcg/g)	Zn
0.00%	(7)	127	0%	0%	15.3	71.6
0.17%	(5)	91	6%	0%	9.4	118.2
0.83%	(9)	45	9%	23%	5.1	168.5
1.66%	(5)	5	19%	100%	0.25	196.3

These results indicate that trientine hydrochloride is teratogenic in rats at dosages similar to those used clinically and that teratogenicity may be due to effects on copper and zinc metabolism. The investigators noted that although it is unlikely that copper deficiency will be induced in Wilson's disease patients on trientine, due to their high copper concentrations at initiation of treatment, these patients are not protected from possibly detrimental effects of high kidney and liver zinc concentrations induced by the drug. The investigators recommended that plasma copper concentrations of pregnant women receiving trientine be monitored along with the copper status of their infants since inadequate copper stores at birth may compromise normal growth and development.

An evaluation similar to that described above was performed with d-penicillamine (another copper chelator) and with a copper deficient (less than 0.5 ppm) diet. The Federation Proceedings abstract (noted above) described the copper deficient diet as being "mildly teratogenic," whereas a diet containing trientine at 1.6% produced a "high frequency of malformations" and a diet containing penicillamine at 0.83% was "highly teratogenic." The abstract goes on to say that tissue copper levels in penicillamine and trientine hydrochloride treated animals were lower than in controls (dose-dependent) and similar in copper deficient diet and 0.83% penicillamine and trientine groups. It was suggested that differences in teratogenic expression might be due to the rate at which maternal plasma copper level is affected. Rapidity of plasma copper decline during pregnancy was greatest for penicillamine and least for the copper deficient diet. Also, the two drugs and the copper deficient diet might affect other trace elements differently. Trientine increased fetal tissue zinc while penicillamine decreased it and the copper deficient diet had little effect. No data was provided on the copper and zinc plasma or tissue analyses carried out in the copper deficient diet group or the penicillamine group.

V. Medical:

- A. Trientine hydrochloride is the established name (also BAN) for triethylene tetramine dihydrochloride [2,2'-ethylene diiminobis (ethylamine) dihydrochloride]. It has also been referred to as Trien.

Wilson's disease, found worldwide, is a rare disease caused by an inherited autosomal recessive abnormality in the hepatic excretion of copper that results in toxic accumulation of the metal in liver, brain and other organs. If untreated, the disease is progressive and fatal, whereas if appropriately treated, the patient may have a normal life and possibly a normal lifespan. Oral penicillamine, a copper chelating agent, has been the drug of choice in the treatment of Wilson's disease. Lifelong treatment is required. If penicillamine cannot be tolerated because of side effects, trientine dihydrochloride is an alternative effective treatment. The following supporting studies indicate that CUPRID is safe and effective for promoting the excretion of copper in pediatric and adult patients intolerant to penicillamine. It is clear from documented historical experience that failure to replace discontinued penicillamine results in return of symptoms and death within a few years. Treatment with trientine hydrochloride prevents most of this morbidity and death.

B. Clinical

Walshe⁽⁷⁾ reported the first successful use of trientine hydrochloride in a 14-year-old boy with Wilson's disease who developed nephrotic syndrome after five and a half years of penicillamine therapy.

A single dose of trientine hydrochloride (one gram) induced a cupriuresis of 2030 ug in 6 hours and treatment with 2.0 gm/day for a week resulted in cupriuresis of 3050 ug/day. Long-term treatment with trientine hydrochloride was initiated, and after 18 months of therapy, sustained clinical improvement was noted with no suggestion of toxicity.

In 1973 Walshe⁽⁸⁾ carried out renal clearance studies 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 (ug Cu ⁺⁺ /6 hr)	Test-dose Excretion Rate (ug Cu ⁺⁺ /6 hr)
6	1.2 g Trientine	19	234
4	500 mg Penicillamine	17	320

In patients not previously treated with chelating agents, a similar comparison was made:

No. of Patients	Treatment	Basal Excretion Rate (ug Cu ⁺⁺ /6 hr)	Test-dose Excretion Rate (ug Cu ⁺⁺ /6 hr)
8	1.2 g Trientine	71	1326
7	500 mg penicillamine	68	1074

These results provide basis for expecting that CUPRID will be effective in the treatment of patients with Wilson's disease.

This NDA includes a summary of the results from 41 patients (18 male and 23 female) between the ages of 6 and 54 who were treated in two separate studies with trientine hydrochloride. The dosage varied from 125 to 2400 mg per day but the dosage required to achieve an optimal clinical response in most patients varied between 900 mg and 1800 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 overall clinical response, 2 were lost to follow-up, 1 showed deterioration in clinical condition, and 1 patient developed lupus erythematosus. No other adverse reactions, except iron deficiency, were noted by any of these 41 patients. The two retrospective clinical studies are summarized as follows:

1. Walshe's Study

Dr. J. M. Walshe studied a total of 31 patients (14 male and 17 female) with trientine dihydrochloride and continued to follow several of them for over 10 years. The total final daily dosage of trientine dihydrochloride ranged from 450 mg to 2400 mg but 27 of the patients received between 900 and 1800 mg as a final dose. Twenty-six patients showed mild to marked global improvement, two demonstrated no change, one became worse, and two were lost to follow-up. Only one of the 31 patients reported an adverse reaction. This patient developed lupus erythematosus syndrome which was considered possibly related to trientine hydrochloride administration.

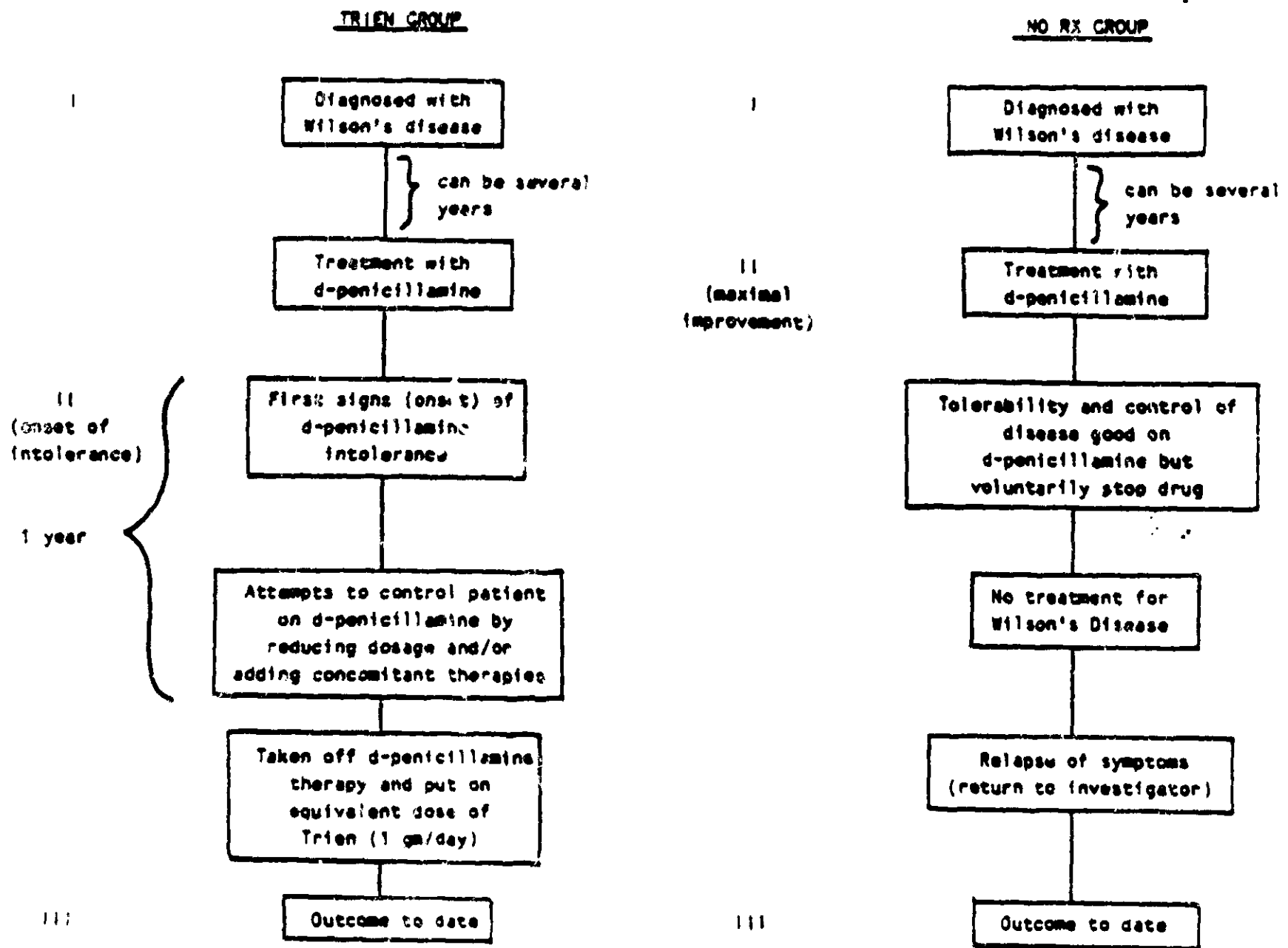
2. Scheinberg's Study

Dr. I. H. Scheinberg has provided data on two groups of patients. One group of 13 patients (including 3 patients whose data became available after the submission of the original NDA), all with a confirmed diagnosis of Wilson's disease, became intolerant to d-penicillamine and were then treated with trientine hydrochloride^a. During the dose titration period, the dosage schedule varied between 500 and 2000 mg daily for a period of 2 to 156 months with final doses usually being 1000 mg/day. One patient required only 0.5 g/day as the maintenance dose. Data were provided for these patients (trientine hydrochloride group) at the time of diagnosis of the disease, at the time of the onset of the d-penicillamine intolerance, and at their last evaluation (a cut-off date of 2/26/85 was used). The other group consists of 12 patients with Wilson's disease who were both tolerant of and controlled on treatment with d-penicillamine, but for various reasons decided to stop d-penicillamine therapy and received no further specific copper chelation therapy. These patients all returned to Dr. Scheinberg's care upon relapse of symptoms. Data were provided for these patients (No Rx group) at the time of diagnosis of the disease, at the time of their maximal improvement while on d-penicillamine treatment, and during their "no treatment" period.

The two groups of patients are different in the selection, i.e., one group (trientine hydrochloride) was investigator selected and the other group (No Rx) was self selected. Also, the trientine hydrochloride group is comprised of patients unable to tolerate d-penicillamine, whereas the No Rx group is comprised of patients who were tolerant of and controlled on d-penicillamine but who decided to stop therapy and continue on no treatment. Table 1 gives a brief summary of a "typical" patient from each group. A summary of the patient characteristics for each group is given in Table 2. The mean age of the patients at the onset of symptoms of the disease was significantly (p less

^a An additional patient who received trientine hydrochloride (#MS4) was excluded from this analysis because he had not received d-penicillamine and therefore should not be included among the patients with previous d-penicillamine intolerance.

TABLE 1: Summary of a "Typical" Patient from Each Group



I, II, III are the three time points at which data was provided for each group.

TABLE 2: Patient Characteristics

<u>PARAMETER</u>		<u>TRIEN GROUP (n=13)</u>	<u>NO RX GROUP (n=12)</u>
Sex:	Female	8	7
	Male	5	5
Age at onset of symptoms: (years)	Mean	21.38	12.00**
	Std. Dev.	11.88	8.33
	Median	18.00	10.00
Duration between onset and d-penicillamine treatment: (years)	Mean	0.77	2.58
	Std. Dev.	1.01	4.38
	Median	0.00	0.00
Duration of d-penicillamine therapy: (years)	Mean	3.96	10.17**
	Std. Dev.	4.50	5.01
	Median	1.00	10.5
Duration of Disease: (years)	Mean	8.81	15.42**
	Std. Dev.	5.91	7.29
	Median	8.00	16.00
Duration between cessation of penicillamine and last observation: (years)	Mean	4.08	2.67
	Std. Dev.	3.86	2.60
	Median	2.00	1.50

** A significant difference between the treatment groups was observed, $p < .01$.

than 0.05) greater in the trientine hydrochloride group (21.4 years) than in the No Rx group (12.0 years). Also, the trientine hydrochloride group had received d-penicillamine treatment for significantly less time than the No Rx group, 4.0 years compared with 10.2 years, respectively. The duration of disease can be thought of as the time between the onset of symptoms and the cut-off date for the data (including time until death). The patients in the trientine hydrochloride group have had Wilson's disease for significantly fewer years (8.8 years) than the No Rx group (15.4 years).

The types of reactions to d-penicillamine in the trientine hydrochloride group which determined the intolerance to the drug are displayed in Table 3. All trientine hydrochloride patients except one (#MS6 is receiving 0.75 gm/day) are receiving 1 gram of trientine hydrochloride per day as the long term maintenance dose.

TABLE 3: Listing of d-Penicillamine Reactions by Patient (Trientine Group Only)

<u>PATIENT NUMBER</u>	<u>NUMBER OF YEARS ON d-PENICILLAMINE</u>	<u>TYPE OF ADVERSE REACTION</u>	<u>DAILY DOSAGE OF d-PENICILLAMINE</u>
MS1	9	Pemphigus	1 gm
MS2	1	Nephrotic	1 gm
MS3	1	Nephrotic	1.25 gm
MS5	1	Thrombocytopenia	1 gm
MS6	7	Nephrotic	1 gm
MS7	1	Nephrotic	1 gm
MS8	15	Elastosis Perforans Serpiginosa	1 gm
MS9	7	Nephrotic	1 gm
MS10	6	Lupus	1 gm
K5	.5	Thrombocytopenia	1 gm
B8	1	Neutropenia	1 gm
K6	1	Nephrotic	1 gm
M16	1	Thrombocytopenia	1 gm

Despite the differences in the two groups of patients with Wilson's disease, it was felt that the two groups in this natural experiment could reasonably be compared statistically using the No Rx group as a reference point and comparing the post-penicillamine results. A formally randomized trial design of drug withdrawal would have been impossible for ethical reasons, and it is known that treated patients generally do well for many years making the duration of disease since diagnosis, and age at onset not so critical. The two groups were evaluated for between and within groups differences. In the trientine hydrochloride group the data available at the time of onset of d-penicillamine intolerance were used as the baseline value and the data from the last evaluation on trientine hydrochloride therapy were used as the treatment value. Similarly in the No Rx group, the data available at time of maximal improvement on d-penicillamine therapy were used as the baseline value and the data from the non-compliance or no treatment period were used as the treatment value. In order to evaluate trientine hydrochloride as an alternative chelating agent for patients with Wilson's disease intolerant of d-penicillamine treatment compared with no treatment, the following parameters were evaluated: free serum copper, total serum copper, SGOT, SGPT, serum bilirubin, serum albumin, ceruloplasmin, Kayser-Fleischer rings, neurological status, psychiatric status, and survival status.

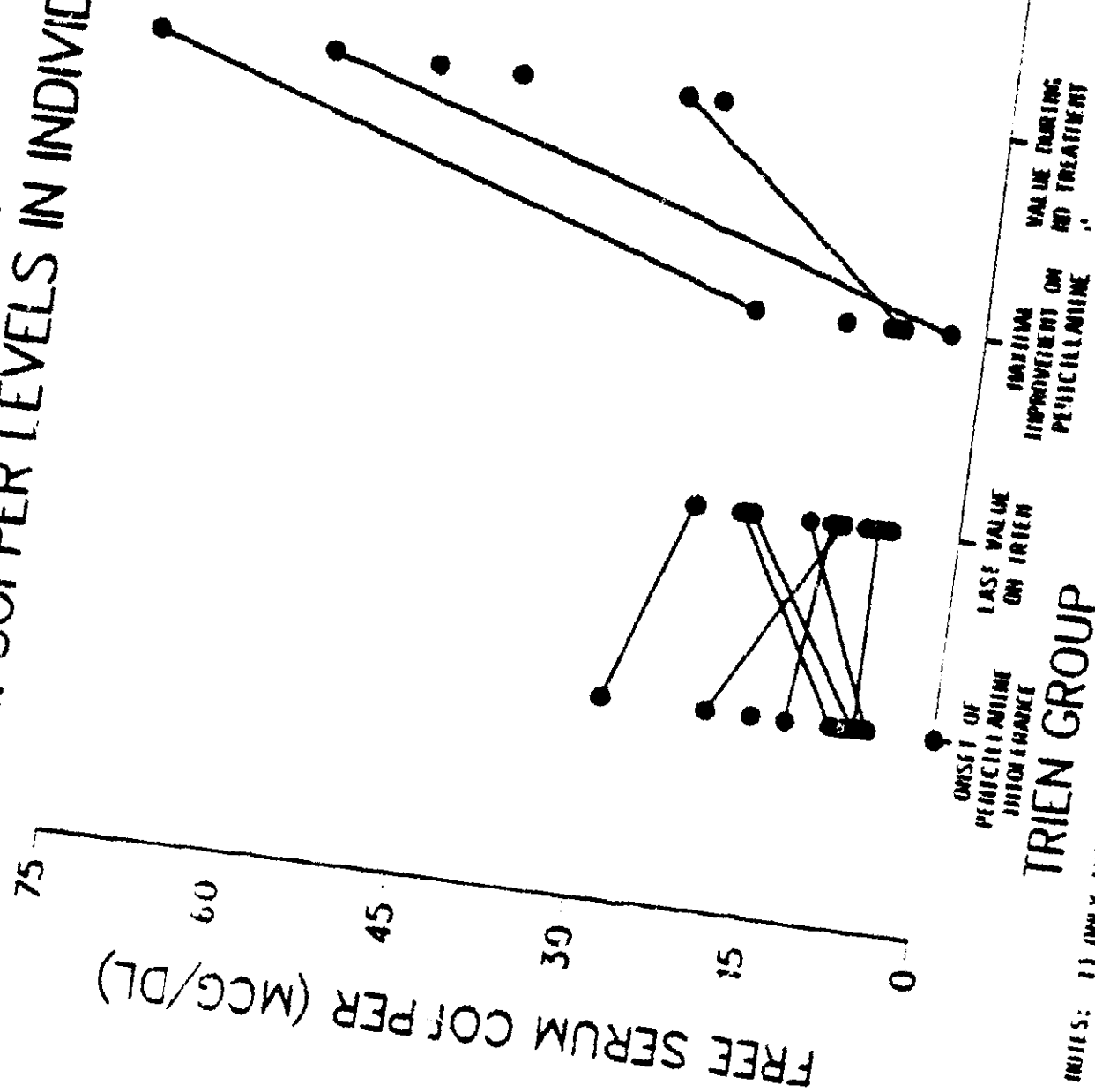
Laboratory Parameters

Fluctuations in the sample size among the various parameters and time points are a result of missing data. The mean values for each continuous laboratory parameter at baseline, treatment, and change from baseline are given in Table 4. The mean values quoted in the text refer to the mean values calculated using all available data at baseline, treatment, or change from baseline.

a. Free Serum Copper

The mean free serum copper levels at baseline were similar for the two groups, 11.5 mcg/dl for the trientine hydrochloride group and 10.0 mcg/dl for the No Rx group. The patients in the trientine hydrochloride group showed a slight mean increase from baseline (1.4 mcg/dl), whereas the patients in the No Rx group had a large mean increase (43.0 mcg/dl) from baseline. The changes from baseline within both groups were not significant, p greater than .25 for the trientine hydrochloride group and p equal to .054 for the No Rx group. The difference between the treatment groups was significant, however, at p less than .01. Free serum copper values for individual patients are given in Figure 1.

FIGURE 1
FREE SERUM COPPER LEVELS IN INDIVIDUAL PATIENTS



NO RX GROUP

INDICES: 1) ONLY THE DATA FROM PATIENTS WHO BOTH THE POINTS WERE CONNECTED WITH A LINE. THE MEAN CHANGING BASAL LINE WAS 1.4 mcg/dL IN THE TRIEN GROUP (n=7) AND 43.0 mcg/dL IN THE NO RX GROUP (n=3).

2) MINIMAL FREE SERUM COPPER IS CONSIDERED TO BE < 10 mcg/dL.

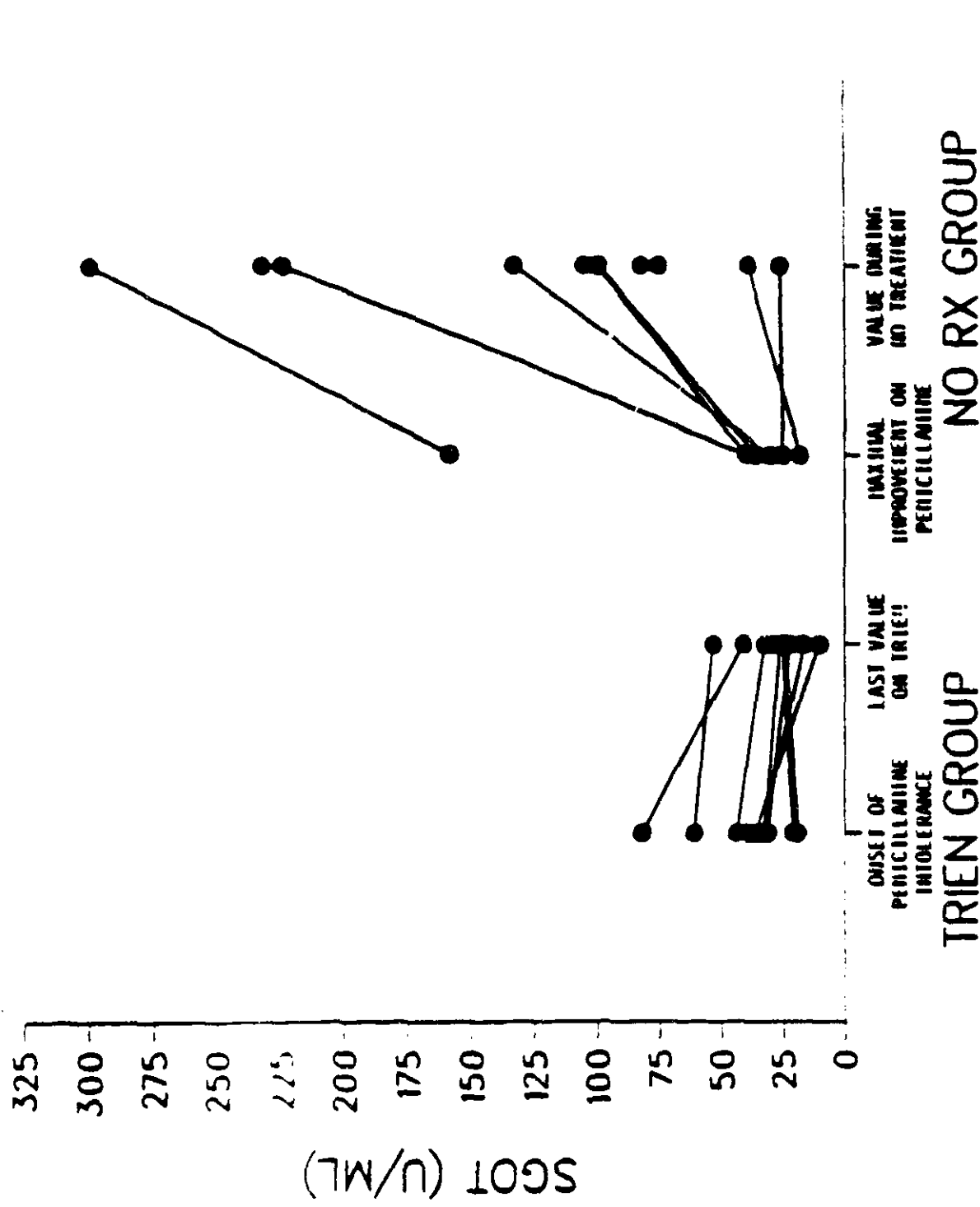
b. Total Serum Copper

Similar trends were observed with regard to the total serum copper measurements. A small, non-significant mean increase (3.1 mcg/dl) from baseline was observed within the trientine hydrochloride group. Within the No Rx group, a large mean increase (57.7 mcg/dl) from baseline was observed. This difference between the groups was significant at p less than .01.

c. SGOT, SGPT

A significant mean decrease from baseline in SGOT was observed within the trientine hydrochloride group (-12.2 u/ml). In contrast, there was a significant mean increase from baseline (82.0 u/ml) within the No Rx group. The difference between the two groups was also significant (p less than .01). Individual patient data is illustrated in Figure 2. Although no significant within the group or between the group differences were observed with regard to SGPT, the overall trends are consistent with those observed for SGOT. The mean SGPT changes from baseline were -7.0 u/ml in the trientine hydrochloride group and 137.7 u/ml in the No Rx group.

FIGURE 2
SGOT LEVELS IN INDIVIDUAL PATIENTS



NOTES: 1) ONLY THE DATA FROM PATIENTS WHO HAD BOTH TIME POINTS WERE CONNECTED WITH A LINE. THE MEAN CHANGE FROM BASELINE WAS -12.2 U/ML IN THE TRIEN GROUP (n=7) and 82.0 U/ML IN THE NO RX GROUP (n=9).
2) NORMAL SGOT IS CONSIDERED TO BE < 40 U/ML.

d. Serum Bilirubin

No mean change from baseline was observed in the trientine hydrochloride group with regard to serum bilirubin. A significant mean increase (9.3 mg/dl) was observed in the No Rx group. This difference was significant between the groups (p less than .01).

e. Serum Albumin

With regard to serum albumin, the trientine hydrochloride group was significantly lower (3.92 gm/dl) at baseline than the No Rx group (4.47 gm/dl). Within the trientine hydrochloride group a significant increase from baseline (0.29 gm/dl) was observed compared with a significant decrease from baseline (-1.87 gm/dl) observed in the No Rx group. The mean change from baseline was significantly different between the groups (p less than .01).

f. Ceruloplasmin

No significant differences between the groups were observed with respect to ceruloplasmin. A smaller mean increase from baseline was observed in the trientine hydrochloride group (1.09 mg/dl) than the No Rx group (4.97 mg/dl) although neither change was significant within the group.

TABLE 4: Mean Laboratory Measurement Values

TIME PERIOD	PARAMETER	TRIEN GROUP			NO RX GROUP			BETWEEN GROUP TEST RESULT
		N	MEAN	STANDARD DEVIATION	N	MEAN	STANDARD DEVIATION	
Pre ^a	Free Serum Copper (mcg/dl)	10	11.50	8.32	5	10.00	6.44	NS(p>.25)
	Total Copper (mcg/dl)	10	23.50	10.98	5	30.20	25.23	NS(p>.25)
	SGOT (u/ml)	10	39.80	18.95	7	49.57	48.49	NS(p>.25)
	SGPT (u/ml)	10	37.10	20.19	5	31.40	16.30	NS(p>.25)
	Serum Bilirubin (mg/dl)	9	0.76	0.32	6	0.53	0.23	NS(p=.124)
	Serum Albumin (gm/dl)	10	3.73	0.61	6	4.47	0.49	*(p=.012)
	Ceruloplasmin (mg/dl)	10	5.81	5.58	6	5.72	8.21	NS(p=.244)
Post ^b	Free Serum Copper (mcg/dl)	10	12.60	5.64	6	45.83	18.24	** (p<.001)
	Total Copper (mcg/dl)	10	23.30	11.06	7	94.29	59.81	** (p<.001)
	SGOT (u/ml)	12	26.50	11.49	11	128.64	86.63	** (p<.001)
	SGPT (u/ml)	10	30.80	24.33	9	106.33	102.24	*(p=.023)
	Serum Bilirubin (mg/dl)	10	0.72	0.43	11	12.42	11.63	** (p<.001)
	Serum Albumin (gm/dl)	11	4.27	0.19	11	2.38	0.48	** (p<.001)
	Ceruloplasmin (mg/dl)	12	6.13	5.35	6	11.23	10.55	NS(p>.25)
Change from Baseline ^c	Free Serum Copper (mcg/dl)	7	1.4	8.1	3	43.0	19.1	** (p=.008)
	Total Copper (mcg/dl)	7	3.1	7.2	3	57.7	42.8	** (p=.008)
	SGOT (u/ml)	9	-12.2 ^Δ	14.4	7	82.0 ^{ΔΔ}	65.3	** (p<.001)
	SGPT (u/ml)	8	-7.0	15.6	4	132.7	134.1	NS(p=.106)
	Serum Bilirubin (mg/dl)	8	0.0	0.4	6	9.3 ^Δ	6.3	** (p=.002)
	Serum Albumin (gm/dl)	8	0.3 ^Δ	0.4	6	-1.9 ^Δ	0.5	** (p<.001)
	Ceruloplasmin (mg/dl)	9	1.1	2.0	3	5.0	10.1	NS(p>.25)

^aPre: 1) This period for the TRIEN group refers to the onset of d-penicillamine intolerance.
 2) This period for the No RX group refers to the maximal improvement observed on d-penicillamine.

^bPost: 1) This period for the TRIEN group refers to the last examination on TRIEN (prior to cutoff date of 12/26/85).
 2) This period for the No Rx group refers to status in non-compliance or during no treatment.

^c Patients had to have both a pre and post measurement in order to be evaluated in the change from baseline analysis.

NS No significant difference was observed with probability p>.05.

* A significant difference was observed with probability p<.05.

** A significant difference was observed with probability p<.01.

Δ, ΔΔ A significant change from baseline was observed within the indicated group, p<.05, p<.01 respectively.

Clinical Parameters

a. Clinical Outcome

The clinical outcome (Table 5) of the patients in the two groups was markedly different. Of the twelve trientine hydrochloride patients, all are still surviving and in the No Rx group nine of the twelve patients died of hepatic disease; this difference was significant at p less than .01. The estimated survival functions for each group are illustrated in Figure 3. The number of years patients received trientine hydrochloride (mean equal to 4.08 years; range of 1 to 13 years) was not significantly different (p equal to .116) from the number of years patients received no therapy (mean = 2.67 years; range of 1/4 to 9 years). In the trientine hydrochloride group, where all of the patients (13) had been intolerant to d-penicillamine therapy (evident by a severe adverse reaction), the adverse reaction disappeared in eight patients, improved in four patients and remained unchanged in one patient (see Table 6).

TABLE 5: Clinical Outcome

<u>GROUP</u>	<u>PATIENT NUMBER</u>	<u>NUMBER OF YEARS AFTER d-PENICILLAMINE^a</u>	<u>CLINICAL OUTCOME OR STATUS</u>
TRIEN	MS1	5	Reaction disappeared; surviving
	MS2	13	Reaction disappeared; surviving
	MS3	2	Reaction disappeared ^b ; surviving
	MS5	6	Reaction improved; surviving
	MS6	11	Reaction disappeared; surviving
	MS7	4	Reaction disappeared; surviving
	MS8	2	Reaction unchanged; surviving
	MS9	3	Reaction improved; surviving
	MS10	2	Reaction disappeared; surviving
	K5	1	Reaction improved; surviving
	B8	1	Reaction improved; surviving
	K6	1	Reaction disappeared; surviving
	M16	2	Reaction disappeared; surviving
NO RX	A2	1	Hepatic decomposition; death
	B4	3	Hepatic decomposition; death
	M1	6	Fulminant hepatitis; death
	R10	.75	Fulminant hepatitis; death
	R9	1	Fulminant hepatitis; death
	B7	3	Fulminant hepatitis; death
	M17	4	Fulminant hepatitis; death
	L9	2	Fulminant hepatitis; death
	S4	1	Neurological status +3; surviving
	P7	.25	Hepatic decomposition; improved cRx; surviving
	S18	1	Hepatic decomposition; transplant; surviving
	WGR	9	Fulminant hepatitis; death

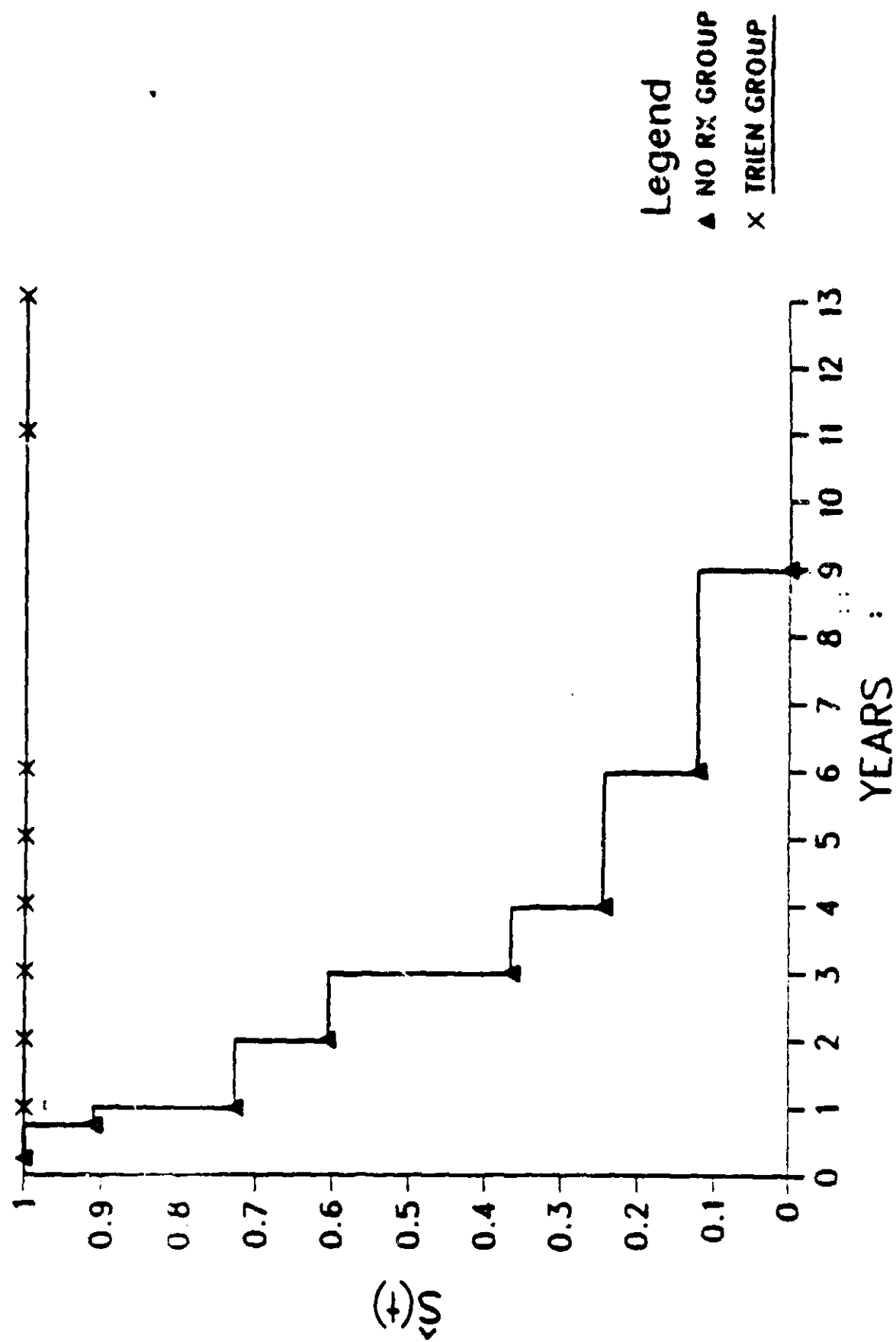
- ^a 1) In the Trien group this refers to the duration on Trien.
 2) In the No Rx group this refers to duration on no therapy.

^b Patient was non-compliant

No significant treatment difference was observed in the mean number of years after d-penicillamine therapy, $p=.115$. The patients in the Trien group received Trien for an average of 4.08 years and the patients in the No Rx group received no therapy for an average of 2.67 years.

A significant treatment difference was observed in the status of survival, $p<.001$. Seventy-five percent of the patients in the No Rx group died compared with 0% in the Trien group.

FIGURE 3: ESTIMATED SURVIVAL FUNCTIONS ($\hat{S}(t)$)



NOTE: $S(t)$ GIVES THE PROBABILITY AN INDIVIDUAL SURVIVES BEYOND TIME t .

TABLE 6

D-Penicillamine Reaction and Outcome (Trien Group Only)

<u>PATIENT NUMBER</u>	<u>TYPE OF d-PENICILLAMINE REACTION</u>	<u>d-PENICILLAMINE REACTION OUTCOME</u>	<u>YEARS TREATED WITH TRIEN</u>
MS1	Pemphigus	Disappeared	5
MS2	Nephrotic	Disappeared	13
MS3	Nephrotic	Disappeared	2
MS5	Thrombocytopenia	Improved	6
MS6	Nephrotic	Disappeared	11
MS7	Nephrotic	Disappeared	4
MS8	Elastosis Perforans Serpiginosa	Unchanged	2
MS9	Nephrotic	Improved	3
MS10	Lupus	Disappeared	2
K5	Thrombocytopenia	Improved	1
B8	Neutropenia	Improved	1
K6	Nephrotic	Disappeared	1
M16	Thrombocytopenia	Disappeared	2

NOTE: All patients are still alive.

b. Neurological Status

Of the 12 trientine hydrochloride patients whose neurological status (Table 7) was recorded at both baseline and treatment, 9 of the patients remained unchanged from baseline (8 of the 9 patients were asymptomatic at both time points) and 2 of the 12 patients had an improvement from baseline. In the No Rx group (12 patients), 6 patients remained unchanged in their neurological status (5 of the 6 patients were asymptomatic at both time points) and the other 6 patients had a worsening from baseline. The two groups were significantly different (p less than .05), in favor of trientine hydrochloride.

TABLE 7: Neurological Symptoms

Distribution of Patients Among Change from Baseline Categories

I. TRIEN GROUP

Category ^a at Onset of d-penicillamine Intolerance	Categories of Change from Baseline					Number of Patients
	Worsening		No Change	Improvement		
	+2	+1	0	-1	-2	
0	0	0	8	0	0	8
1	0	1	0	0	0	1
2	0	0	1	1	0	2
3	0	0	0	0	1	1
4	0	0	0	0	0	0
—	—	—	—	—	—	—
Total	0	1	9	1	1	12

II. NO RX GROUP

Category ^a at Time of Maximal Improvement on d-penicillamine	Categories of Change from Baseline					Number of Patients
	Worsening		No Change	Improvement		
	+2	+1	0	-1	-2	
0	0	6	5	0	0	11
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	1	0	0	1
4	0	0	0	0	0	0
—	—	—	—	—	—	—
Total	0	6	6	0	0	12

^a Categories ranged from 0 to 4 with 0 = asymptomatic and 4 = patient can barely talk, uses a cards to communicate, considerable drooling, extreme difficulty swallowing, can not walk.

No significant treatment difference was observed in the distribution of patients among the baseline categories, $p=.158$.

A significant treatment difference was observed in the distribution of patients among the change from baseline categories, $p=.015$.

c. Psychiatric Status

With regard to the psychiatric status (Table 8) of the patients, all of the patients in the trientine hydrochloride group either remained unchanged from baseline (8/11 patients were asymptomatic at both time points) or improved relative to baseline. All of the patients in the No Rx group were reported as asymptomatic. This is questionable, however, because each patient voluntarily stopped taking d-penicillamine knowing that the treatment was required in controlling their fatal disease. Ten of the 12 patients remained unchanged (asymptomatic) after no treatment and 2 of the patients experienced a worsening. No significant difference between the treatment groups was observed with respect to the distribution of patients among the categories of change from baseline, but a treatment difference was observed at baseline (p less than .05).

TABLE 8: Psychiatric SymptomsDistribution of Patients Among Change from Baseline CategoriesI. TRIEN GROUP

Category ^a at Onset of d-penicillamine Intolerance	Categories of Change from Baseline					Number of Patients
	Worsening		No Change	Improvement		
	+2	+1	0	-1	-2	
0	0	0	8	0	0	8
1	0	0	2	1	0	3
2	0	0	0	0	0	0
3	0	0	1	0	0	1
4	0	0	0	0	0	0
—	—	—	—	—	—	—
Total	0	0	11	1	0	12

II. NO RX GROUP

Category ^a at Time of Maximal Improvement on d-penicillamine	Categories of Change from Baseline					Number of Patients
	Worsening		No Change	Improvement		
	+2	+1	0	-1	-2	
0	2	0	10	0	0	12
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
—	—	—	—	—	—	—
Total	2	0	10	0	0	12

^a Categories ranged from 0 to 4 with 0 = asymptomatic and 4 = patient is "off the wall", has sexual inappropriateness, and psychotic breaks.

A significant treatment difference was observed in the distribution of patients among the baseline categories, $p=.047$.

No significant treatment difference was observed in the distribution of patients among the change from baseline categories, $p=.130$.

d. Kayser-Fleischer Ring

The Kayser-Fleischer ring is a golden-brown or gray-green pigment ring that appears at the corneal limbus due to copper deposition in Descemet's membrane. In general, the Kayser-Fleischer rings (Table 9) were significantly more prominent in the trientine hydrochloride group than in the No Rx group at baseline. When evaluating the distribution of patients with regard to their change from baseline, of the patients who showed a change, the trientine hydrochloride group improved whereas the No Rx group worsened. This difference was significant (p less than .05).

TABLE 9: Kayser-Fleischer Rings
Distribution of Patients Among Change from Baseline Categories

I. TRIEN GROUP

Category ^a at Onset of d-penicillamine Intolerance	Categories of Change from Baseline								Number of Patients	
	Worsening				No Change	Improvement				
	+4	+3	+2	+1	0	-1	-2	-3		-4
0	0	0	0	0	2	0	0	0	0	2
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	2	0	0	0	2
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	2	0	1	0	1	4
	—	—	—	—	—	—	—	—	—	—
Total	0	0	0	0	4	2	1	0	1	8

II. NO RX GROUP

Category ^a at Time of Maximal Improvement on d-penicillamine	Categories of Change from Baseline								Number of Patients	
	Worsening				No Change	Improvement				
	+4	+3	+2	+1	0	-1	-2	-3		-4
	<u>+4</u>	<u>+3</u>	<u>+2</u>	<u>+1</u>	<u>0</u>	<u>-1</u>	<u>-2</u>	<u>-3</u>		<u>-4</u>
0	1	1	0	0	3	0	0	0	0	5
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	1	0	0	0	0	1
	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>
Total	1	1	0	0	4	0	0	0	0	6

^a Categories ranged from 0 to 4 in increasing severity.

A significant treatment difference was observed in the distribution of patients among the baseline categories, $p=.008$.

A significant treatment difference was observed in the distribution of patients among the categories of change from baseline, $p=.023$.

D. Conclusions

1. Trientine hydrochloride is an effective chelating agent for copper as demonstrated by both in vitro and animal studies.
2. Trientine hydrochloride is an effective agent in pediatric and adult patients with Wilson's disease, preventing the rapidly progressive course of that disease when infocated.
3. Trientine hydrochloride is well tolerated, and no severe or serious adverse experiences have been reported.

VI. Approved Package Insert:

A copy of the package insert is attached.

VII. REFERENCES

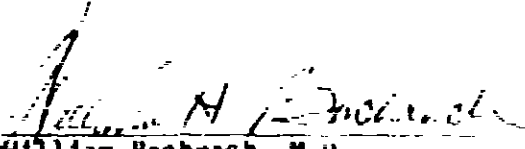
1. Borthwick RR, Benson GD, Schugar HJ: A Comparison of Cupriuretic Responses to Various Tetramines and d-Penicillamine. J Lab Clin Med 95 (4):575-580, Apr 1980.
2. Dubois RS, Rodgenson DO, Slovis TL, Hambidge KM and Bianchi TA: Triethylene Tetramine Dihydrochloride in Wilson's Disease. Lancet 2:775, Oct 10, 1970.
3. Gibbs K, Walshe JM: The Effects of Certain Chelating Compounds on the Urinary Excretion of Copper by the Rat: Observations on Their Clinical Significance. Clinical Science and Molecular Medicine 53: 317-320, 1977.
4. Jackson GE, May PM, Williams DR: The Action of Chelating Agents in the Removal of Copper from Ceruloplasmin. Febs Lett 90(1): 173-177, June 1978.
5. May PM, Williams DR: Computer Models of Metal Ion-Low Molecular Weight Equilibria in Plasma and the Influence of d-penicillamine, Triethylenetetramine and EDTA. Proc Roy Soc Med 70 (Supl 3): 19-23, 1977.
6. Planas-Bohne, F: Influence of Several Chelating Agents on the Excretion and Organ Concentration of Copper in the Rat. Tox and Applied Pharm 50:337-345, 1979.
7. Walshe JM: Management of Penicillamine Nephropathy in Wilson's Disease: A New Chelating Agent. Lancet 2:1401-1402, Dec 27, 1969.
8. Walshe JM: Copper Chelation in Patients with Wilson's Disease: A Comparison of Penicillamine and Triethylene Tetramine Dihydrochloride. Quart J Med 42(167): 441-452, July 1973.

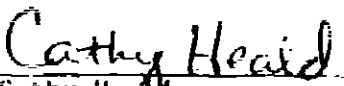
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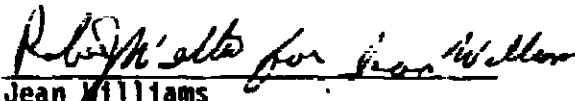
Cuprid


Raymond J. Lipicky, M.D.
Acting Division Director

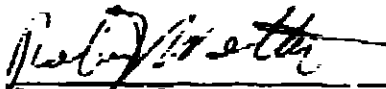

Charles Resnick, Ph.D.
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Medical Officer


Cathy Heald
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Supervisory Consumer Safety
Officer


Robert Wolters, Ph.D.
Supervisory Chemist

cc:
Orig.
HFN-110
HFN-110/FOI (3)
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HF-35/Rüregorio
0550N

CAPSULES

MSD | **CUPRID®**
 (TRIENTINE HYDROCHLORIDE, MSD)

CUPRID®
 (Trientine Hydrochloride, MSD)

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 $C_6H_{16}N_4 \cdot 2HCl$ with a molecular weight of 219.2. The structural formula is:



Trientine hydrochloride is a chelating compound for removal of excess copper from the body. CUPRID® (Trientine Hydrochloride, MSD) is available as 250 mg capsules for oral administration. Capsules CUPRID contain stearic acid as an inactive ingredient.

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

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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 there 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

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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 ($\mu\text{g Cu}^{++}/\text{hr}$)	Test-dose Excretion Rate ($\mu\text{g Cu}^{++}/\text{hr}$)
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 ($\mu\text{g Cu}^{++}/\text{hr}$)	Test-dose Excretion Rate ($\mu\text{g Cu}^{++}/\text{hr}$)
8	Trientine, 1.2 g	71	1326
7	Penicillamine, 500 mg	68	1074

These results demonstrate that CUPRID 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

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

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

CUPRID is not indicated for treatment of biliary cirrhosis.

CONTRAINDICATIONS

Hypersensitivity to this product.

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WARNINGS

Patient experience with trientine hydrochloride is limited (see CLINICAL PHARMACOLOGY). Patients receiving CUPRID 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 CUPRID 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 CUPRID. 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 CUPRID each inhibit absorption of the other, two hours should elapse between administration of CUPRID and iron.

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It is important that CUPRID 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

Pregnancy Category C. 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. CUPRID 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 CUPRID is administered to a nursing mother.

Pediatric Use

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

ADVERSE REACTIONS

Clinical experience with CUPRID has been limited. The following adverse reactions have been reported in patients with Wilson's disease who were on therapy with trientine hydrochloride: iron deficiency, systemic lupus erythematosus (see CLINICAL PHARMACOLOGY).

CUPRID 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.

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It is important that CUPRID 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.

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 CUPRID is 500 - 750 mg/day for children 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 children age 12 or under. The daily dose of CUPRID 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 CUPRID 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

No. 3511 — Capsules CUPRID, 250 mg, are light brown opaque capsules and are coded MSD 679. They are supplied as follows:

NDC 0006-0679-68 in bottles of 100.

Storage

Keep container tightly closed.

Store at 2° - 8°C (35.6° - 46.4°F).

MSD MERCK SHARP & DOHME
DIV. OF MERCK & CO., INC., WEST POINT, PA. 19382, USA

NDA

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178

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 19-194

Name of Drug: Trientine Dihydrochloride (Trien)

Sponsor: Merch Sharp & Dohme

Date of Submission: October 2, 1984

Date Received by Medical Officer: October 10, 1984

Date Reviewed: October 22, 1984

Reviewer: William H. Bachrach, M.D.

Formulation: Capsules

Route of Administration: Oral

Proposed Clinical Use: Treatment of Wilson's Disease

Material Reviewed: Summary of basis for approval.

Evaluation: This SBA follows the conventional format and represents accurately the clinical characteristics of the drug, as documented in my review of the NDA in January of this year.

Recommendation: The medical part of the SBA is acceptable.

William H. Bachrach, M.D.

cc: Orig. NDA 19-194

HFN-110

~~HFN-110/CSO~~

HFN-110/HHBachrach 10-22-84

rq: 10-27-84:0001r

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Medical Officer's Review

NDA 19-194

DRUG: Trien (Trientine Dihydrochloride)

SPONSOR: Merck, Sharpe & Dohme Research Laboratories

PROPOSED CLINICAL USE: Treatment of Wilson's Disease.

FORMULATION: Capsules 250 mg.

ROUTE OF ADMINISTRATION: Oral.

DATE OF SUBMISSION: December 30, 1983.

MATERIAL SUBMITTED: This NDA consists of 4 volumes, the second of which deals with chemistry and manufacturing.

DATE RECEIVED BY MEDICAL OFFICER: January 9, 1984.

DATE REVIEWED: April 9, 1984.

MATERIAL REVIEWED: Vols 1, 3 and 4, dealing with clinical data.

REVIEWED BY: William H. Bachrach, M.D.

I. BACKGROUND AND RATIONALE:

Wilson's disease is caused by an impairment of hepatic excretion of copper, resulting in toxic accumulation of the metal in liver, brain and other organs. A characteristic laboratory finding is a deficiency of the plasma protein, ceruloplasmin, an alpha-2 globulin which binds copper. The disease may present clinically as an asymptomatic hepatosplenomegaly, as acute hepatitis or cirrhosis, or, in exceptional cases, as a neurological or psychiatric disturbance. Unless the copper excess in the body is reduced pharmacologically, the disease follows a progressive downhill course and is eventually fatal.

Until recently the drug of choice for this disease has been D-penicillamine, a copper chelating agent. Administration of this drug may be associated with serious side effects such as granulocytopenia, thrombocytopenia, nephrotic syndrome, systemic lupus erythematosus or myasthenia gravis. These effects may be sufficiently severe to require permanent discontinuation of the drug, leaving the patient no alternative therapy. The sponsor presents evidence that trientine dihydrochloride is an effective and safe alternative therapy.

II. CLINICAL PHARMACOLOGY

Information is limited to that reported by Walshe (Copper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride. Quart J Med 42:441-452, 1973). The essential data are displayed in Table 1, which is a comparison of the primary parameters of copper metabolism in patients receiving Trien without and with pre-treatment with penicillamine. This comparison is appropriate because almost every patient who receives Trien will have been on a trial of penicillamine therapy. It is clear that Trien exerts its favorable effect by removing deposits of copper from body tissues. In the process, there is no effect on the level of copper in the serum, presumably because of the very efficient renal clearance of copper which in turn results in an enormous increase in the urinary copper content. After prolonged treatment with penicillamine, during which the patient has obviously been "de-coppered", the copper-chelating action of Trien is much diminished, but, as is evident from the data on renal clearance, is still sufficient to prevent re-accumulation of copper in the tissues.

Walshe hypothesizes that there may be two pools of copper, one stable (or firmly attached to tissue protein) and one labile. In untreated patients the labile pool is large and both chelating agents can readily mobilize this copper. However, when treatment has been given for long enough to deplete this pool, Trien proves less effective for removing copper from the stable pool. Any further speculation is idle, considering the paucity of the data.

III. EFFECTIVENESS:

Clinical studies: The sponsor did not initiate and/or subsidize the clinical trials reported herein. They were carried out independently by two recognized experts in the field. The sponsor was able to obtain the detailed records of the cases and to transfer the data to case report forms for inclusion in this NDA. Placebo-controlled studies were not done because they would be flagrantly unethical in this disease.

A. STUDY NO. 1 (Study conducted under [REDACTED])

1. Investigator: I. Herbert Scheinberg, M.D.
Albert Einstein College of Medicine
New York, NY 10461

2. Procedure:

a. Objective: To evaluate the effects of treatment with Trien in patients with confirmed Wilson's disease in whom adverse experiences were associated with administration of penicillamine.

II. CLINICAL PHARMACOLOGY

Information is limited to that reported by Walshe (Copper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride. Quart J Med 42:441-452, 1973). The essential data are displayed in Table 1, which is a comparison of the primary parameters of copper metabolism in patients receiving Trien without and with pre-treatment with penicillamine. This comparison is appropriate because almost every patient who receives Trien will have been on a trial of penicillamine therapy. It is clear that Trien exerts its favorable effect by removing deposits of copper from body tissues. In the process, there is no effect on the level of copper in the serum, presumably because of the very efficient renal clearance of copper which in turn results in an enormous increase in the urinary copper content. After prolonged treatment with penicillamine, during which the patient has obviously been "de-coppered", the copper-chelating action of Trien is much diminished, but, as is evident from the data on renal clearance, is still sufficient to prevent re-accumulation of copper in the tissues.

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A. STUDY NO. 1 (Study conducted under [REDACTED])

1. Investigator: I. Herbert Scheinberg, M.D.
Albert Einstein College of Medicine
New York, NY 10461

2. Procedure:

- a. Objective: To evaluate the effects of treatment with Trien in patients with confirmed Wilson's disease in whom adverse experiences were associated with administration of penicillamine.

b. Study population: Ten patients, 6F and 4M, ages 17 to 54 years, in whom the duration of illness ranged from 2.4 to 24 years, who had been treated with penicillamine in doses ranging from 500 to 2000 mg/day for periods ranging from 9 to 173 months.

c. Plan of treatment: The usual starting dose was 1000 mg/day taken in the form of 250 mg capsules; adjustments to the dosage were made when necessary on the basis of determinations of the serum and urinary copper levels.

3. Results (Table 2):

Most patients were stabilized on a daily dose of 1000 mg. The duration of treatment varied from 2 to 125 months. The drug was clinically effective in 8/10, ineffective in 2/10. In none of the patients were any adverse effects experienced.

B. STUDY NO. 2

1. Investigator: J. M. Walshe, Sc.D.
Department of Medicine
University of Cambridge
Addenbrooke's Hospital
Cambridge, England

2. Procedure:

a. Objective, procedure, and plan of treatment were as in the study cited above.

b. Study Population: Thirty-one patients, 17F, 14M, ranging in ages from 6 to 50 years. Only one of the patients had not been previously been treated with penicillamine; the duration of treatment in the other cases varied from 2 weeks to 194 months. All of the patients previously treated with penicillamine were selected for a trial with Trien because of adverse effects of penicillamine.

3. Results (Table 3): Duration of treatment with Trien varied from 2 to 164 months in doses (as adjusted at the time of this submission) ranging from 450 to 2400 mg/day. Among the 31 patients, the drug was clinically effective in 26 (84%), ineffective in 3 (9%) and the outcome was unknown in 2 (6%). Adverse effects were reported in only one patient (i.e., the patient became worse on treatment and the clinical deterioration was therefore considered an adverse effect). Since no information was available on the outcome of treatment in 2 of the patients, the incidence of adverse effects in this series should be appropriately based on 29 patients, giving an incidence of 3%.

C. COMBINED RESULTS OF THE TWO CLINICAL TRIALS (Table 4): Among the 41 patients treated, the drug was clinically effective in 34 (83%), ineffective in 5 (12%) and no information concerning the clinical outcome was available in 2 (5%). Adverse effects were reported in only one patient (3%). Thus the effectiveness of Trien treatment in patients experiencing adverse effects during treatment with penicillamine is clearly demonstrated.

D. REPORTS FROM THE LITERATURE

1. Results in the treatment of Wilson's disease (Table 5): Results of treatment have been reported in 6 cases in 5 reports. Sufficient information is available in these reports to permit the conclusion that in at least 4 of the patients (67%) the treatment was effective. An adverse effect (increased excretion of zinc in the urine) was reported in 1 of the 6 cases.

2. Results of treatment in other diseases in which penicillamine has been found to be effective (Table 6):

Not only was Trien ineffective in rheumatoid arthritis and in primary biliary cirrhosis, but in the former series, its administration was accompanied by deterioration in biochemical parameters of rheumatoid activity, while in the latter Trien treatment was accompanied by severe adverse effects.

E. CONCLUSION REGARDING EFFECTIVENESS:

The evidence supports the conclusion that Trien is effective in the treatment of patients with Wilson's disease in whom penicillamine therapy must be discontinued because of adverse effects. The drug has been found to be ineffective and productive of adverse effects in rheumatoid arthritis and primary biliary cirrhosis. Thus, at the present time, the only indication for Trien therapy is in the treatment of patients with Wilson's disease in whom treatment with penicillamine becomes untenable because of adverse effects.

IV. SAFETY

A. CLINICAL LABORATORY STUDIES

1. Hematology: No clinically important changes in hematological parameters (hemoglobin, hematocrit, white blood count, differential count, platelets) attributable to the test drug were observed.

2. Biochemistry: No clinically important changes attributable to Trien were observed in the total protein, albumin, calcium, phosphorus, urea nitrogen, bilirubin, creatinine, glucose, sodium or potassium.

3. Tests of Liver Injury: No sustained abnormalities, certainly none requiring interruption of treatment, were observed in the alkaline phosphatase, SGOT or SGPT.
 4. Serum Iron: In the series of Dr. Walshe, low values were observed in 4 patients, all menstruating females, requiring temporary decrease in the dosage of Trien and the administration of iron supplements or improvement in the diet.
 5. Serum Ceruloplasmin: As expected, consistent with the pathologic physiology of Wilson's disease, the levels remained consistently below normal in all patients.
 6. Serum Copper: All reported baseline levels were below normal and remained low throughout treatment. This is also a consistent finding in Wilson's disease.
 7. Urinary Copper: Elevated copper excretion was maintained throughout the study, which was, obviously, the purpose of the treatment and the mechanism by which clinical improvement is obtained.
 8. Urinalysis: None of the values for specific gravity, glucose or protein were consistently abnormal or were considered attributable to Trien therapy.
- B. EVIDENCE FROM THE CLINICAL TRIALS REPORTED IN THIS SUBMISSION: The fact that therapy with Trien had to be discontinued in only 1 of 41 patients attests to a favorable safety profile.
- C. EVIDENCE FROM THE PUBLISHED LITERATURE:
1. Walshe (An assessment of the treatment of Wilson's disease with triethylene tetramine 2HCl (Trien 2HCl). In: Biological aspects of metals and metal-related diseases, Sarkar B (ed), Raven Press, New York, 1983, chap. 19) reports the following observations relating to safety:
 - a. Among his patients there were 1 father and 3 mothers, 2 of whom had 2 children, and all the children were normal.
 - b. One patient took almost a month's supply of the drug in a single dose (approximately 30 grams) and suffered no apparent ill effects. This patient is one of the mothers who had 2 successful pregnancies, one before and one after the drug overdose.

- c. There has been no evidence of marrow depression or hepatotoxicity.
 - d. Two patients developed lupus nephritis possibly attributable to Trien.
 - e. Long term treatment showed a tendency to induce an iron-deficiency anemia responsive to treatment with oral iron preparations.
 - f. An alarming worsening of the neurological deficit was observed in one patient at the start of treatment with Trien.
 - g. There have been 5 successful pregnancies in patients taking Trien at the time of conception and throughout pregnancy.
2. In a letter to Lancet, Dubois et al reported a significant increase in the urinary excretion of zinc in a patient receiving Trien, suggesting a potential zinc depletion.

D. CONCLUSION REGARDING SAFETY:

As with all other drugs, the full safety profile of Trien will not become apparent until extensive marketing experience becomes available. This will probably take many more years than is ordinarily the case, probably decades, considering (a) the comparatively low prevalence of Wilson's disease (probably not exceeding 5,000 cases in the U.S.), and (b) the very small proportion (of the order of 2%) of these patients who are intolerant to penicillamine, the primary treatment.

V. PACKAGE INSERT:

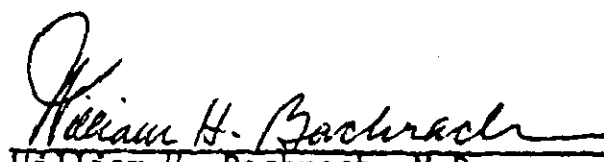
The label is generally satisfactory. Sponsor's attention should be called to suggestions for the following relatively minor revisions.

- A. CLINICAL PHARMACOLOGY: ". . . elevating the amount of copper in the blood. . . ." The available data do not support this part of the statement, even as a speculation (see Table 1).
- B. INDICATIONS AND USAGE: Change to ". . . treatment of patients with Wilson's disease who are unable to tolerate treatment with penicillamine."
- C. PREGNANCY: Before the last sentence, insert: "However, 5 successful pregnancies with normal offspring have been recorded in 3 patients receiving Trien at the time of conception and throughout pregnancy."

VI. SUMMARY:

This NDA requests approval for marketing of Trien (trientine dihydrochloride capsules) as an alternative therapy in the treatment of Wilson's disease. As evidence of safety and effectiveness of the drug, the sponsor submits results of treatment in a total of 41 patients, 40 of whom had become intolerant to the primary treatment (penicillamine) and would have been left without any resource for survival had not this alternative treatment become available on an investigative basis. Trien maintained the patients in effective remission in 83% of the cases with a possible adverse effect (general deterioration) in only one (3%) of the patients. The therapeutic effect is achieved by a mechanism similar to that of penicillamine, namely, chelation of copper. Data from the literature suggest that the safety profile may not be as clean as it appears from the study in this small series of patients but this is not a matter of great concern because the benefit:risk ratio overwhelming favors the approval of this product in view of the seriousness of the disease for which it is indicated. The package insert accurately conveys the information relevant to the effective and safe use of the drug, with possibly a few minor deficiencies subject to revision.

VII. RECOMMENDATION: Expeditious approval of this orphan drug.


William H. Bachrach, M.D.

cc: Orig. NDA 19-194
HFN-110
~~HFN-110/CSO~~
HFN-110/WHBachrach
rq:4-15-84:4-24-84:5784c

NDA

19-194

Pharm Rev

NDA 19-194

Trientine Dihydrochloride

Merck Sharp & Dohme

Review and Evaluation of Pharmacology and Toxicology Data
Original Summary

Category: chelating agent, oral

Composition: Capsules, 250 mg

Indication: treatment of Wilson's Disease in penicillamine-intolerant patients

Related [REDACTED]

Summary and Evaluation

Sponsor has submitted this NDA in response to the Federal Register Notice of September 24, 1982 which invited the submission of an NDA for the use of trientine dihydrochloride in penicillamine-intolerant patients with Wilson's Disease.

This is considered an orphan drug since there are an extremely small number of patients (in the hundreds) for whom the drug is indicated. Since this is an orphan drug NDA, the customary preclinical pharmacology and toxicology data is not necessary and was not submitted with the NDA.

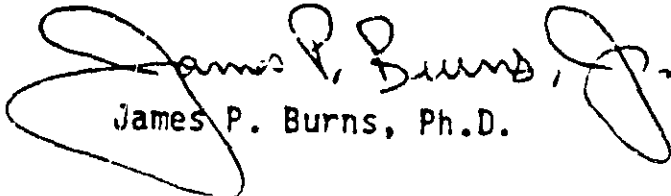
The condition for which this drug is indicated, i.e., Wilson's Disease, is an inherited autosomal recessive abnormality in the hepatic excretion of copper that results in toxic accumulation of copper in tissues including the brain (causing neurologic manifestations such as resting and intention tremors, spasticity, rigidity, chorea, drooling, dysphagia and dysarthria) and the liver (which can lead to acute hepatitis, cirrhosis, or asymptomatic hepatosplenomegaly). Left untreated, Wilson's Disease causes progressive deterioration of the patient leading to death due to intolerance of excess copper being deposited in tissues throughout the body. Thus, some form of pharmacologic intervention is necessary to stay the course of the disease.

For many years, the drug of choice for treating Wilson's disease has been D-penicillamine, a copper chelating agent that removes excess copper from the blood. This is a lifetime therapy and for most patients it is an acceptable form of therapy. However, in about 10% of patients some form of immunologically-induced intolerance to penicillamine develops sooner or later; the most serious being immune-complex nephritis, systemic lupus erythematosus, hemolytic anemia, and a condition with symptoms closely mimicking those of Goodpastures syndrome. For these penicillamine-intolerant patients, an alternative form of therapy, trientine dihydrochloride, has been available for about 15 years. This drug has been effective and, with the limited clinical experience available, has caused minimal or no adverse reactions. Trientine dihydrochloride apparently acts differently than d-penicillamine in that it appears to mobilize tissue copper, elevating the amount of copper in the blood, which leads to increased renal excretion of copper.

Although the customary preclinical pharmacology/toxicology studies are not contained in this NDA, the nature of the submission and the condition for which it is indicated would make such a requirement unnecessary. There was a literature report submitted (Keen, et al., Lancet (8281): 1127, 5/15/82) that showed trientine dihydrochloride to be teratogenic (resorptions, fetal edema and hemorrhaging) at oral doses as low as 0.17% of trientine in the diet (about 8.5 mg/kg) which is below the maximum recommended adult dose. This information is included in the package insert. Additional preclinical toxicology studies are being conducted at NCTR (90448) studies in rats and mice) and will be submitted in the future, but should not affect action on approval of this NDA.

Recommendation

This NDA would be approvable from Pharmacology as an orphan drug to treat penicillamine-intolerant patients with Wilson's Disease.


James P. Burns, Ph.D.

cc:

~~HFN-110~~

HFN-110/CSO

HFN-110/JPBurns

gm/7-11-84/Wang 7190c

NDA

19194

Chem

REUs

SEP 25

CHEMIST'S PART - SBA for TRIEN

NDA #: 19-194 Cuprid (Trien - triethylenetetramine dihydrochloride)
250 mg Capsule

Applicant: Merck Sharp and Dohme Research Labs
Division of Merck and Company Inc.
West Point, PA 19486

III. Manufacturing and Controls

- A. The description of the preparation and purification of the dihydrochloride salt from Trien base is described in sufficient detail in the Eastman-Kodak and Aldrich Chemical Co.'s DMFs 5351 and 1796, to determine the validity of the assigned chemical structure and to confirm the suitability of the specifications and test methods for the bulk drug substance.

The controls over the manufacturing procedures, which include specifications and test methods for the new drug substance, the excipients and the finished dosage form, give sufficient assurance of the identity, strength, quality and purity of the drug.

B. Stability Studies

The stability data submitted is adequate to support the proposed 18 month expiration date, showing that the strength, identity, quality and purity of the drug will be maintained throughout this period. Suitable provisions and appropriate commitments have been made for the continued monitoring of representative samples of the drug and submission of supporting data as it becomes available.

- C. Analytical methods for both the bulk drug substance and the finished dosage form have been validated by an FDA Laboratory. Difficulties were encountered in the method for the Capsules and a revised method will be sent for revalidation.

D. Labeling

The immediate container labels for the 250 mg Capsules packaged in HDPE bottles with metal screw caps are in compliance with requirements pertaining to the following:

Proprietary name, non-proprietary name, ingredient statement, control number, prescription caution, applicant's name and address, storage statement and net contents statement.

The package insert is satisfactory in regard to both the DESCRIPTION and HOW SUPPLIED sections. The trade name of the drug is not in conflict with the name of any other drug.

E. Establishment Inspection

A memorandum from the Drug Manufacturing Branch dated March 1, 1984 and confirmed by the Drug Alert List, stated that there is no reason to withhold approval of this NDA with respect to the type of operations specified in the NDA when conducted by the following firms:

Bulk Drug Manufacturer:

Eastman-Kodak Co.
Rochester, N.Y. 14650

Applicant/Manufacturer
Dosage Form

Merck Sharp and Dohme Research Laboratories
Division of Merck and Company, Inc.
West Point, PA 19486

F. Environmental Impact Analysis Report

A report is included in the original application for this drug which states that there will be no adverse effect on the environment produced by the manufacture of this product.

The disposal of gaseous and solid wastes generated in the manufacturing facilities is controlled in accordance with local and federal regulations.

H 1 1 10

Jean Williams
Jean Williams

OCT 19 1984

REVIEW AND EVALUATION OF MANUFACTURING CONTROLS DATA

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Chemist's Review # 3

Date Completed: 10/17/84

Date of Submission: 10/11/84

NDA 19-194

Cuprid
Merck Sharp and Dohme Research Laboratories
Division of Merck and Company Inc.
West Point, PA 19436

The following information is included in this submission:

1. The tradename, Cuprid is introduced for this copper chelating compound, Trien, triethylenetetramine dihydrochloride.
2. Specifications are included for both Trien raw material and capsules (see attached sheet).
3. Two TLC methods are included for the determination of impurities in Trien raw material. Dr. Picot, in a telephone conversation between him, myself and Helen Shaw, MSD QC, recommended that Method II be sent for validation. In that method, specs for DETA (diechyenetriamine) are NMT 1.0%, total other impurities NMT 1.0%. Therefore specs for impurities are NMT 2.0%. MSD will be asked about the trihydrochloride of Trien. Dan Botesky of Eastman Kodak, in a telephone conversation on 8/2/84, stated that there are two different assay specs for Trien: 100-104% by AgNO_3 titration, in which both Trien and the trihydrochloride are titrated and 98-101% for the CuNO_3 titration method. (These were Eastman Kodak specs).
4. A CuNO_3 titration method is submitted for the assay of Trien raw material. Specs are 97-103%. MSD validation of this method is included. This method is also being sent to 2 FDA Labs for validation.
5. A test for capsule Content Uniformity, based on the weight of full and empty capsules is included.
6. A capsule dissolution test which uses the following parameters is included:
USP II (paddle), water, 50 RPM, assay- Cu complex colorimetric method. Spec NLT 80% in 30'.

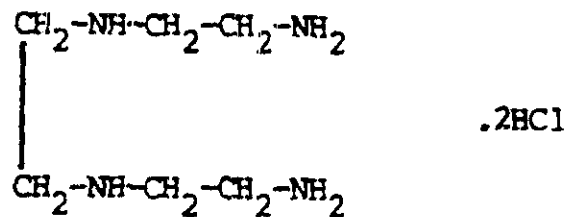
Specifications - Bulk Chemical

Trientine dihydrochloride

[2,2' ethylene diiminobis(ethylamine) dihydrochloride]

$C_6H_{18}N_4 \cdot 2HCl$

Mol Wt. 219.16



Physical Description: A white to pale yellow crystalline powder.

<u>Test</u>	<u>Proposed Specification</u>
1. Assay (Copper Titration)	97-103%
2. Loss on Drying	Max 2%
3. Residue on Ignition	Max 0.15%
4. Heavy Metals	Max 10 ppm
5. pH (1% Solution)	7.0 to 8.5
6. Infrared	Conforms
7. Impurities by TLC	Method I and *Method II
	DETA: Max 1% Total other impurities: Max 1%

*Preferred method for detection of impurities

Finished Product Specifications

Appearance: A light brown opaque hard gelatin capsule #1

Dose Uniformity: Conforms to USP XX requirements for dose uniformity

Trientine Dihydrochloride: 250 mg/capsule
(225-275 mg/capsule)

Dissolution: Conforms to USP - 80% in 30 min

Test Methods

Test methods for the above are attached.

7. The following stability data is included:

Triethylenetetramine dihydrochloride

2 lots from Eastman-Kodak stored up to 8 months at R.T.
Single spots are noted in the TLC test up to 2 months;
after that, two spots are noted.

MSD also included on page 30, the degradation pathway for triethylenetetramine. Under conditions of heat and moisture, Trien degrades to DETA (diethylenetriamine) which then degrades to ethylenediamine.

Trien Capsules

1 lot made from raw material from Aldrich for capsules stored up to 64 weeks at R.T., 5°C and 30°C. Dissolution values are also included.

All data submitted is within the 90-110% potency spec and the NLT 80% in 30' dissolution spec. However, after 64 weeks at 30°C, Per cent potency = 95.2, while samples stored at R.T. and 5°C are 100.0%.

A one year expiration date with capsules stored under refrigeration, is to be assigned to this product until further data is obtained.

2 lots of Trien Capsules made from raw material from Eastman-Kodak and stored up to 52 weeks at R.T., 5°C and 30°C at ambient R.H. are also reported.

Capsule contents show discoloration after 52 weeks at 30°C. One sample stored for 52 weeks at 30°C and ambient R.H. showed no discoloration but both samples stored for 52 weeks at 75% R.H. showed discoloration and potency losses of 21.6 and 40.2%.

8. Information is also included regarding the comparison of values obtained under stressed and non-stressed conditions for Trien raw material assayed by both the colorimetric and GC assay methods. Values obtained by the two methods are almost identical for initial and stressed conditions for 7, 23 and 180 days.

The GC assay looks like a very good method. It is more sensitive and linearity. Detection of 2 impurities have been demonstrated. MSD state, however, that a different column must be used to obtain the reproducibility needed for a control method.

The CuNO_3 titration method and the colorimetric assay for Trien raw material and capsules respectively were sent to Edro today (10/16/84).

As methodology validation results are no longer needed for NDA approval, this NDA will probably be approved before validation results are obtained. This is because pressure is being put on this Division by the Division of Orphan Drug Products to approve it. This compound is considered an advance over penicillamine for the treatment of Wilson's disease, as patients develop adverse reactions (including SLE) after long term treatment with penicillamine.

It should be safe to approve this drug as raw material impurities are now at MIT 2.0% and the breakdown products, diethylenetriamine and ethylene diamine should now be any more toxic than Trien, their chelation power is just lower (about 1/2 and 1/6 respectively).

John Williams

cc: OMS
 1+FN-110
 1+FN-110/CSO
 1+FN-110/Williams

REVIEW AND EVALUATION OF MANUFACTURING CONTROLS DATA

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

CHEMIST'S REVIEW # 6

Date Completed: 10-4-85

A. 1. NOA # 19-194

Applicant: Merck Sharp and Dohme Research Laboratories
Division of Merck and Company, Inc.

Address: West Point, Pa 19486

AF #:

2. Product Name

Proprietary - Cuprid

Nonproprietary Trientine dihydrochloride

USAN -

Compendium -

Code Name and/or Number -

3. Dosage Form and Route of Administration: (R_x or OTC)

Oral capsules - R_x

4. Pharmacological Category and/or Principal Indication:

Chelating agent - to be used to remove excess copper ions from organs of patients suffering from Wilson's Disease who are intolerant to penicillamine.

The following information is included in this submission:

Results of TLC method for Trientine Hydrochloride received from BLT-DO showed lower Rf values for impurities than those reported by MSD.

	MSD	BLT-DO Stds	NDS
Tren	0		
Trientine	.17		.10
DETA	.26	.16	.17
EDA	.36	.28	.26
AEPZ	.36	.30, .29	
BAPZ	.60		

.46

Since values obtained by BLT-DO analyst for EDA and AEPZ were very close in value identification of impurity present at Rf .26 is questionable. BLT-DO analyst will to repeat the validation and in addition use a "spiked" sample.

TLC method for related substances received from DHSS.UK will be sent to lab. for validation.

MSD TLC method needs directions for preparation of EDA standard solution.

Byworth
10/17/00

Daniel A. Cunningham

OMP

HFN-110

HFN-110/ESU

HFN-110/DGC

NDA 19-194

November 15, 1985

Addendum to Chemist's Review # 6

TLC results for Trientine HCl were received from Philadelphia District.

	Philadelphia		Baltimore		MDS
	<u>NDS</u>	<u>STDS</u>	<u>NDS</u>	<u>STDS</u>	<u>STDS</u>
Tren	0				0
Trientine	0.06	0.06	0.10	0.11	0.17
DETA	0.13	0.13	0.17	0.16	0.26
EDA				0.28	0.36
AEPZ		0.21		0.30	0.56
		0.48		0.29	
BAPZ					0.60
Unknowns	0.30		0.46		
	0.60				

Rf values for standards were lower in each laboratory from the values obtained by MDS.

Philadelphia District Laboratory estimated impurity level at about 2%. They obtained poor separation between tren, trientine and DETA., same as seen in the original TLC evaluation. No copy of TLC received. For standard B the analyst in Philadelphia District weighed out only AEPZ but had two spots, Rfs 0.21 and 0.48. I wonder if EDA was also included in the preparation of the standard solution.

The company will be asked to either improve the TLC procedure or develop a new method for the detection and separation of the impurities.

Danute G. Cunningham
Danute G. Cunningham

Orig.
HFN-110
HFN-110/CSO
HFN-110/DGC