CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-194/S005

APPROVAL LETTER

FEB - 8 2000

NDA 19-194/S-005

Merck & Co., Inc.
Attention: Dennis M. Erb
Sumneytown Pike
P.O. Box 4
BLA-20
West Point, PA 19486

Dear Dr. Erb:

Please refer to your supplemental new drug application dated August 25, 1999, received August 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Syprine™ (trientine hydrochloride) Capsules.

We acknowledge receipt of your submission dated September 29, 1999.

This "Changes Being Effected" supplemental new drug application provides for changes in the ADVERSE REACTIONS section of the package insert to include dystonia, muscular spasm, and myasthenia gravis.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/ 2-8-00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 19-194
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: A.Kacuba/February 7, 2000
Final: A.Kacuba/February 8, 2000 (S1) 2-8-2000
Filename: c:\mydocuments\19194-S-005-AP.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-194/S005

APPROVABLE LETTER

NDA 19-194/S-005

SEP 2 3 1999

Merck & Company, Inc.
Attention: Dennis M. Erb, Ph.D.
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

Dear Dr. Erb:

We acknowledge receipt of your manufacturing supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SYPRINE™ (trientine hydrochloride) Capsules

NDA Number: 19-194

Supplement Number: S-005

Date of Supplement: August 25, 1999

Date of Receipt: August 27, 1999

This supplement proposes the following change: Revisions to the ADVERSE REACTIONS section of the package insert to add dystonia, muscular spasm, and myasthenia gravis. Your submission stated February 1, 2000 as the implementation date for the change.

We note that you have submitted these supplements under 21 CFR 314.70(c), 'Special Supplement - Changes Being Effected.'

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on October 24, 1999 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be February 27, 2000.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/S/ 9-23-99

Alice Kacuba, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 19-194/S-005
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/Reviewers and Team Leaders
HFD/180 M. Kidwell
DISTRICT OFFICE
Drafted by: mk 9/1/99
Initialed by: A. Kacuba 9/9/99
final: M. Kidwell 9/9/99
filename:

SUPPLEMENT ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-194/S005

FINAL PRINTED LABELING

MERCK & CO., INC.
West Point, PA 19486, USA

7664603

NDA 19-194/S-005

CAPSULES
SYPRINE®
(Trientine Hydrochloride)

DESCRIPTION

Trientine hydrochloride is *N,N'*-bis (2-aminoethyl)-1,2-ethanediamine dihydrochloride. It is a white to pale yellow crystalline hygroscopic powder. It is freely soluble in water, soluble in methanol, slightly soluble in ethanol, and insoluble in chloroform and ether.

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

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

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

CLINICAL PHARMACOLOGY

Introduction

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

Clinical Summary

Forty-one patients (18 male and 23 female) between the ages of 6 and 54 with a diagnosis of Wilson's disease and who were intolerant of d-penicillamine were treated in two separate studies with trientine hydrochloride. The dosage varied from 450 to 2400 mg per day. The average dosage required to achieve an optimal clinical response varied between 1000 mg and 2000 mg per day. The mean duration of trientine hydrochloride therapy was 48.7 months (range 2-164 months). Thirty-four of the 41 patients improved, 4 had no change in clinical global response, 2 were lost to follow-up and one showed deterioration in clinical condition. One of the patients who improved while on therapy with trientine hydrochloride experienced a recurrence of the symptoms of systemic lupus erythematosus which had appeared originally during therapy with penicillamine. Therapy with trientine hydrochloride was discontinued. No other adverse reactions, except iron deficiency, were noted among any of these 41 patients.

One investigator treated 13 patients with trientine hydrochloride following their development of intolerance to d-penicillamine. Retrospectively, he compared these patients to an additional group of 12 patients with Wilson's disease who were both tolerant of and controlled with d-penicillamine therapy, but who failed to continue any copper chelation therapy. The mean age at onset of disease of the latter group was 12 years as compared to 21 years for the former group. The trientine hydrochloride group received d-penicillamine for an average of 4 years as compared to an average of 10 years for the non-treated group.

Various laboratory parameters showed changes in favor of the patients treated with trientine hydrochloride. Free and total serum copper, SGOT, and serum bilirubin all showed mean increases over baseline in the untreated group which were significantly larger than with the patients treated with trientine hydrochloride. In the 13 patients treated with trientine hydrochloride, previous symptoms and signs relating to d-penicillamine intolerance disappeared in 8 patients, improved in 4 patients, and remained unchanged in one patient. The neurological status in the trientine hydrochloride group was unchanged or improved

over baseline, whereas in the untreated group, 6 patients remained unchanged and 6 worsened. Kayser-Fleischer rings improved significantly during trientine hydrochloride treatment.

The clinical outcome of the two groups also differed markedly. Of the 13 patients on therapy with trientine hydrochloride (mean duration of therapy 4.1 years; range 1 to 13 years), all were alive at the data cutoff date, and in the non-treated group (mean years with no therapy 2.7 years; range 3 months to 9 years), 9 of the 12 died of hepatic disease.

Chelating Properties

Preclinical Studies

Studies in animals have shown that trientine hydrochloride has cupriuretic activities in both normal and copper-loaded rats. In general, the effects of trientine hydrochloride on urinary copper excretion are similar to those of equimolar doses of penicillamine, although in one study they were significantly smaller.

Human Studies

Renal clearance studies were carried out with penicillamine and trientine hydrochloride on separate occasions in selected patients treated with penicillamine for at least one year. Six-hour excretion rates of copper were determined off treatment and after a single dose of 500 mg of penicillamine or 1.2 g of trientine hydrochloride. The mean urinary excretion rates of copper were as follows:

No. of Patients	Single Dose Treatment	Basal Excretion Rate (µg Cu + + /6hr)	Test-dose Excretion Rate (µg Cu + + /6hr)
6	Trientine, 1.2 g	19	234
4	Penicillamine, 500 mg	17	320

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

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

These results demonstrate that SYPRINE 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

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

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

SYPRINE is not indicated for treatment of biliary cirrhosis.

CONTRAINDICATIONS

Hypersensitivity to this product.

WARNINGS

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

It is important that SYPRINE 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. SYPRINE 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 SYPRINE is administered to a nursing mother.

Pediatric Use

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

ADVERSE REACTIONS

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

SYPRINE 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.

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 SYPRINE is 500-750 mg/day for pediatric patients and 750-1250 mg/day for adults given in divided doses two, three or four times daily. This may be increased to a maximum of 2000 mg/day for adults or 1500 mg/day for pediatric patients age 12 or under. The daily dose of SYPRINE 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 SYPRINE 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. 3408 — Capsules SYPRINE, 250 mg, are light brown opaque capsules coded SYPRINE on one side and MSD 661 on the other. They are supplied as follows:

NDC 0006-0661-68 in bottles of 100
(6505-01-321-5213, 250 mg 100's)

Storage

Keep container tightly closed.
Store at 2-8°C (36-46°F).

Dist.by
MERCK & CO., INC., West Point, PA 19486, USA

Issued May 1999
Printed in USA

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-194/S005

MEDICAL REVIEW(S)

FEB - 7 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	19-194/SLR-005
SPONSOR:	Merck Laboratories
DATE SUBMITTED:	August 25, 1999
DRUG:	Capsules SYPRINE™ (trientine hydrochloride)
INDICATION:	Treatment of Wilson's Disease in Patients Intolerant to Penicillamine
REVIEWER:	Steven Aurecchia, MD /S 2/5/00

The sponsor has conducted a review of its worldwide adverse event reports database and has added the following underlined text to the ADVERSE REACTIONS section of the approved package insert for this product. These changes will become effective on or about February 1, 2000 [Changes Being Effected]:

ADVERSE REACTIONS

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

SYPRINE 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.

COMMENT:
These labeling changes are based on case reports in three patients. In each case, causality is somewhat difficult to assess. The reported events were temporally related to SYPRINE treatment; however, confounding factors may also have played a role (this was difficult to evaluate based on the limited information presented). None of the patients were re-challenged with SYPRINE.

RECOMMENDATION:
Approval of the Labeling Supplement as submitted.

CC:
NDA Arch. 19-194
HFD-180
HFD-180/LTalarico /S 2-7-00
HFD-180/SAurecchia
HFD-180Gallo-Torres
HFD-180/AKacuba

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-194/S005

ADMINISTRATIVE DOCUMENTS

FEB - 8 2000

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 19-194/S-005

Name of Drug: Syprine (trientine hydrochloride) Capsules

Sponsor: Mereck Research Laboratories

Material Reviewed

Submission Date(s): August 25, 1999, Electronic Final Printed Labeling

Receipt Date(s): August 27, 1999

Background and Summary Description: NDA 19-194; Syprine (trientine hydrochloride) Capsules is approved for the treatment of patients with Wilson's disease who are intolerant of penicillamine. Supplement -005 (Special Supplement—Changes Being Effected) proposes the addition of dystonia, muscular spasm and myasthenia gravis to the ADVERSE REACTIONS section of the package insert.

Review

Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines.

Package insert

The submitted package insert identified as "7664603 Issued May 1999" was compared to the labeling found acceptable in Annual Report –010, identified as "7664601 Issued March 1989".

1. The second sentence of the first paragraph of the ADVERSE REACTIONS section has been revised as follows:

   "The following adverse reactions have been reported in a clinical study in patients with Wilson's disease who were on therapy with Trientine hydrochloride: iron deficiency, systemic lupus erthematosus (see CLINICAL PHARMACOLOGY).

Comment: This revision is an appropriate editorial revision.

2. The first paragraph of the ADVERSE REACTIONS section has been revised to read:

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

Comment: The Medical Officer Review dated February 7, 2000, found this revision acceptable.

3. The HOW SUPPLIED section has been revised as follows:

   "No. 3408 — Capsules SYPRINE, 250 mg, are light brown opaque — coded SYPRINE on one side and MSD 661 on the other. They are supplied as follows:
   NDC 0006-0661-68 in bottles of 100
   (6505-01-321-5213, 250 mg 100's)"

Comment: The addition of the debossing of SYPRINE on the one side is an acceptable revision. The other revisions are acceptable editorial revisions.

4. The identifier at the top of the labeling has been revised as follows:

   "766460-2"

5. The revision date has been revised as follows:

   "Issued ——— May 1999"

Comment: These are appropriate editorial revisions.

Conclusions

The submitted labeling is acceptable and the supplement can be approved.
The currently approved labeling is now considered:

Package insert: "7664603"
Bottle label: "7757602"
Carton: "7664701"

/S/ 2-8-2000
Regulatory Health Project Manager

/S/ 2-8-00
Division Director

APPEARS THIS WAY
ON ORIGINAL