**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 copper into the bile. Hepatocytes store excess copper but when their capacity is exceeded copper is released into the blood and is taken up by extracellular 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 treatment 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 of clinical condition. One of the patients who withdrew from 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 the 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 but were 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 48.7 months; range 2-164 months), 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 larger.

**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:

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Single Dose Treatment</th>
<th>Basal Excretion Rate</th>
<th>Test-dose Excretion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trientine, 1.2 g</td>
<td>(µg Cu + + /6hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Penicillamine, 500 mg</td>
<td>(µg Cu + + /6hr)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>234</td>
<td>320</td>
</tr>
</tbody>
</table>

These results demonstrate that trientine is effective as a cupriuretic agent in patients with Wilson’s disease although on a molar basis it appears to be less potent or less effective than penicillamine. Evidence from a radio-labelled copper study indicates that the different cupriuretic effects of the 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 alterations in laboratory parameters have not been well-characterized in defining an individual patient’s dose has 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 iron deficiency 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**

Patients who switch from trientine hydrochloride to the human dose. The frequencies of both resorptions and fetal abnormalities, including hemorrhage and edema, increased while fetal copper levels were as follows:

No. of Patients | Single Dose Treatment | Basal Excretion Rate | Test-dose Excretion Rate |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trientine, 1.2 g</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Penicillamine, 500 mg</td>
<td>(µg Cu + + /6hr)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>68</td>
<td>1074</td>
</tr>
</tbody>
</table>

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

Geriatric Use
Clinical studies of Syprine did not include sufficient numbers of subjects aged
65 and over to determine whether they respond differently from younger
subjects. Other reported clinical experience is insufficient to determine
differences in responses between the elderly and younger patients. In
general, dose selection should be cautious, usually starting at the low end
of the dosing range, reflecting the greater frequency of decreased hepatic,
renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Clinical experience with 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.

To report SUSPECTED ADVERSE REACTIONS, contact Valeant
Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at
1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE
There is a report of an adult woman who ingested 30 grams of trientine
hydrochloride without apparent ill effects. No other data on overdose
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 300-750 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
Syprine capsules, 250 mg, are light brown opaque capsules coded SYPRINE
on one side and ATON 710 on the other. They are supplied as follows:

NDC 0187-2120-10 in bottles of 100.

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

Manufactured for:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Valeant Pharmaceuticals International, Inc.
Steinbach, MB R5G 1Z7 Canada

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