Overview

This policy supports medical necessity review for trientine hydrochloride (Syprine®).

Medical Necessity Criteria

Trientine hydrochloride (Syprine®) is considered medically necessary when the following are met:

1. **Wilson’s Disease.** Individual meets **ALL** of the following criteria (A, B, and C):
   A. Documented diagnosis of Wilson’s disease as evidenced by **ONE** of the following (i or ii):
      i. Genetic testing results confirming biallelic pathogenic ATP7B mutations (in either symptomatic or asymptomatic individuals)
      ii. At least **TWO** of the following:
         a. Presence of Kayser-Fleischer (KF) rings
         b. Serum ceruloplasmin levels less than 20mg/dL
         c. Liver biopsy findings consistent with Wilson disease
         d. 24-hour urinary copper is greater than 40 μg/24 hours
   B. Individual meets **ONE** of the following criteria (i, ii, iii, or iv):

i. Individual has a documented contraindication per FDA label, significant intolerance, or is not a candidate* for penicillamine therapy (Cuprimine®, Depen®, or generics)
ii. Individual has neurologic manifestations of Wilson's disease
iii. Individual is pregnant
iv. Individual has been started on therapy with trientine (Syprine)

C. The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician

*Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], other attributes/conditions, or is unable to administer and requires this dosage formulation. Examples may include: history of renal disease, congestive splenomegaly causing severe thrombocytopenia, or autoimmune tendency

Coverage for trientine hydrochloride (Syprine) varies across plans and may require the use of preferred products in addition to the medical necessity criteria listed above. Refer to the customer’s benefit plan document for coverage details.

When coverage requires the use of preferred products, there is documentation of ONE of the following:

A. The individual has had inadequate efficacy to the number of covered alternatives according to the table below

OR

B. The individual has a contraindication according to FDA label, significant intolerance, or is not a candidate* for the covered alternatives according to the table below

*Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], other attributes/conditions, or is unable to administer and requires this dosage formulation)

Employer Group Non-Covered Products and Preferred Covered Alternatives by Drug List:

<table>
<thead>
<tr>
<th>Non-Covered Product</th>
<th>Standard / Performance</th>
<th>Value / Advantage</th>
<th>Cigna Total Savings</th>
<th>Legacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syprine (trientine hydrochloride)</td>
<td>trientine hydrochloride³</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

³Documentation that individual has tried the bioequivalent generic product AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction

#Prior authorization may apply

Individual and Family Plan Covered Alternatives:

<table>
<thead>
<tr>
<th>Non-Covered Product</th>
<th>Covered Alternative(s)</th>
</tr>
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³Documentation that individual has tried the bioequivalent generic product AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction.

#Prior authorization may apply

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.
Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Trientine hydrochloride is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up to 12 months.

Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Trientine hydrochloride is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. Biliary Cirrhosis.
   Trientine (Syprine, generics) is not indicated for the treatment of biliary cirrhosis.¹

2. Cystinuria.
   Trientine (Syprine, generics) is not recommended for use in individuals with cystinuria.¹ Unlike penicillamine, trientine does not contain a sulfhydryl moiety and therefore it is not capable of binding cysteine.

3. Rheumatoid Arthritis (RA).
   Trientine (Syprine, generics) is not recommended for use in individuals with RA.¹ Per the prescribing information, trientine was not found to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment of individuals with RA.

Background

OVERVIEW
Trientine, a metal chelator, is indicated for the treatment of patients with Wilson’s disease who are intolerant of penicillamine.¹ Trientine and penicillamine are not interchangeable; trientine should be used when treatment with penicillamine is no longer possible because of intolerable or life-endangering side effects. Trientine is not indicated for use in patients with cystinuria, rheumatoid arthritis, or biliary cirrhosis. In general, patients should remain under regular medical supervision while receiving trientine and patients (especially women) should be closely monitored for evidence of iron deficiency anemia. Controlled studies of trientine in pediatric patients are not available; however, it has been used in patients as young as 6 years with no adverse events. Other chelating agents indicated in the treatment of Wilson’s disease include penicillamine capsules (Cuprimine®, generics) and Depen® (penicillamine tablets).⁵⁶ These agents also have other indications for the treatment of cystinuria and treatment of patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy.

Disease Overview
Copper is an essential metal and is an important cofactor for many proteins.³ However, normal dietary consumption and absorption of copper exceeds the amount that the body needs.⁴ Copper homeostasis depends primarily on biliary excretion. Wilson’s disease is an inherited disorder in which alterations in cellular copper processing and impaired biliary excretion lead to copper accumulation.²⁴ Copper initially builds up in the liver and eventually is released into the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea). The majority of patients with Wilson’s disease are diagnosed between the ages of 5 and 35 years, with
the most common presentations being liver disease, neurological disorder (e.g., tremor, ataxia, dystonia), or psychiatric illness.\textsuperscript{3-4} The average prevalence of Wilson’s disease is 30 cases per million individuals. Lifelong pharmacologic therapy is the mainstay of treatment for Wilson’s disease; without treatment, most patients will die from liver disease or progressive neurologic disease. Liver transplantation is reserved for severe or resistant cases. In patients with Wilson’s disease, trientine acts as a general metal chelator and promotes urinary copper excretion.

Guidelines
The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson’s disease (2008).\textsuperscript{3} It is noted that while the most experience in the treatment of this condition is with penicillamine, trientine is effective for the treatment of Wilson’s disease, especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency).

Trientine has been found to be effective initial therapy, even in patients with decompensated liver disease at the outset. The AASLD recommends that initial treatment for symptomatic patients include a chelating agent (penicillamine or trientine). Neurological worsening following therapy initiation appears to be much less common with Syprine than with penicillamine. For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options. Zinc appears preferable for presymptomatic children under the age of 3 years. In pregnant patients, treatment for Wilson’s disease should be continued due to the risk of liver failure with therapy interruption, but dosage reduction is advisable for penicillamine and trientine. Satisfactory outcomes have been shown with continuation of therapy with chelating agents (both penicillamine and trientine) during pregnancy. Liver transplantation should be considered in patients with acute liver failure due to Wilson’s disease and in patients with decompensated cirrhosis unresponsive to chelation therapy.

The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson’s disease (2012).\textsuperscript{4} Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. The EASL also notes that trientine has been shown to be an effective initial therapy. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients, and again, a chelating agent or zinc may be used for the treatment of presymptomatic patients or patients established on maintenance therapy. In patients with neurological disease established on maintenance therapy either a chelating agent or zinc may be used; zinc may have a role as first-line therapy in these patients. The EASL guidelines also state that despite teratogenicity concerns with penicillamine, treatment of Wilson’s disease should be continued during pregnancy as the risks of withdrawing therapy outweigh those of continuing therapy. However, penicillamine and trientine dosage reductions are recommended in pregnant patients.

References

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