Prior Authorization
Chelating Agents - Syprine® (trientine hydrochloride capsules, generics)

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National Formulary Medical Necessity

Cigna covers trientine hydrochloride products (Syprine®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior authorization is recommended for prescription benefit coverage of trientine (Syprine, generics). Because of the specialized skills required for evaluation and diagnosis of individuals treated with trientine (Syprine, generics) as well as the monitoring required for AEs and long-term efficacy, initial approval requires trientine (Syprine, generics) to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below.

FDA Indication(s)

1. **Wilson’s Disease.** Approve for 3 years if the individual meets the following criteria (A and B):
   A) Individual meets ONE of the following criteria (i, ii, iii, iv, v or vi):
      i. Individual has tried one penicillamine product and is intolerant to penicillamine therapy, according to the prescriber; OR
      Note: Examples of penicillamine products are Cuprimine® (penicillamine capsules, generics), Depen® (penicillamine tablets, generics).
ii. Individual has clinical features indicating the potential for intolerance to penicillamine therapy, according to the prescriber; OR
   Note: Specific clinical features include history of any renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency.

iii. Individual has a contraindication to penicillamine therapy, according to the prescriber; OR

iv. Individual has neurologic manifestations of Wilson’s disease; OR

v. Individual is pregnant; OR

vi. Individual has been started on therapy with trientine (Syprine, generics).

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

### Conditions Not Covered

Trientine hydrochloride (Syprine®) 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 individuals 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 individuals with cystinuria, rheumatoid arthritis, or biliary cirrhosis. In general, individuals should remain under regular medical supervision while receiving trientine and individuals (especially women) should be closely monitored for evidence of iron deficiency anemia. Controlled studies of trientine in pediatric individuals are not available; however, it has been used in individuals 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).⁵-⁶ These agents also have other indications for the treatment of cystinuria and treatment of individuals 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 individuals 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.³⁴ 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 individuals will die from liver disease or progressive neurologic disease. Liver transplantation is reserved for severe or resistant cases. In individuals 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 individuals 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 individuals with decompensated liver disease at the outset. The AASLD recommends that initial treatment for symptomatic individuals 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 individuals 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 individuals, 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 individuals with acute liver failure due to Wilson’s disease and in individuals 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 individuals, and again, a chelating agent or zinc may be used for the treatment of presymptomatic individuals or individuals established on maintenance therapy. In individuals 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 individuals. 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 individuals.

**References**


**Revision History**

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<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
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<tbody>
<tr>
<td>Annual Revision</td>
<td>No criteria changes.</td>
<td>09/23/2020</td>
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