



PRIOR AUTHORIZATION POLICY

- POLICY:** Chelating Agents – Trientine Products Prior Authorization Policy
- Cuvrior™ (trientine tetrahydrochloride tablets – Orphalan)
 - Syprine® (trientine hydrochloride capsules – Bausch, generic)

REVIEW DATE: 11/15/2023

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Trientine products (capsules [Syprine, generics] and tablets [Cuvrior]) are chelating agents indicated for the treatment of **Wilson's disease** (hepatolenticular degeneration).^{1,2}

Syprine (trientine hydrochloride capsules, generic) is indicated for the following use:¹

- Treatment of patients with **Wilson's disease** who are intolerant of penicillamine.

Cuvrior (trientine tetrahydrochloride tablets) is indicated for the following use:²

- Treatment of adults with stable **Wilson's disease** who are de-coppered and tolerant to penicillamine.

Trientine is not indicated for use in patients with cystinuria, rheumatoid arthritis, or biliary cirrhosis.¹ Trientine products should be used when treatment with penicillamine is no longer possible because of intolerable or life-endangering side effects.¹ The content of trientine differs between products, thus they are not interchangeable on a mg per mg basis.²

Disease Overview

Wilson's disease is an autosomal recessive disorder in which alterations in cellular copper processing and impaired biliary excretion lead to copper accumulation.³⁻⁵ Copper initially builds up in the liver and is eventually released into the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea) so it can cause a wide variety of symptoms. 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 as well as blocks dietary copper absorption.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2022).⁴ Diagnosis of Wilson's disease is confirmed by conducting genetic testing confirming biallelic pathogenic *ATP7B* mutations or confirmation of at least two clinical features associated with Wilson's disease (Kayser-Fleischer rings, serum ceruloplasmin level < 20 mg/dL, liver biopsy, 24-hour urinary copper > 40 mcg/24 hours). The AASLD recommends a chelating agent (penicillamine or trientine) for initial treatment of symptomatic patients. For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options.

The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson's disease (2012).⁵ Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients, and 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. If zinc is used, careful monitoring of transaminases is needed, with changing to chelators if these laboratory parameters are increasing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of trientine products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trientine as well as the monitoring required for adverse events and long-term efficacy, approval requires trientine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Cuvrior™ (trientine tetrahydrochloride tablets – Orphalan)**
- **Syprine® (trientine hydrochloride capsules – Bausch, generic)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. Wilson's Disease. Approve for 1 year if the patient meets the following (A, B, and C):

A) Diagnosis of Wilson's disease is confirmed by ONE of the following (i or ii):

- i. Genetic testing results confirming biallelic pathogenic *ATP7B* mutations (in either symptomatic or asymptomatic individuals); OR
- ii. Confirmation of at least TWO of the following (TWO of a, b, c, or d):
 - a) Presence of Kayser-Fleischer rings;
 - b) Serum ceruloplasmin level < 20 mg/dL;
 - c) Liver biopsy findings consistent with Wilson's disease;
 - d) 24-hour urinary copper > 40 mcg/24 hours; AND

B) Patient meets ONE of the following (i, ii, iii, iv, v or vi):

- i. Patient 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, generic), Depen (penicillamine tablets, generic).
- ii. According to the prescriber, patient has clinical features indicating the potential for intolerance to penicillamine therapy; OR
Note: Specific clinical features include history of any renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency.
- iii. Patient has a contraindication to penicillamine therapy, according to the prescriber; OR
- iv. Patient has neurologic manifestations of Wilson's disease; OR
- v. Patient is pregnant; OR
- vi. Patient has been started on therapy with trientine (Cuvrior or Syprine, generic).

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

CONDITIONS NOT COVERED

- **Cuvrior™ (trientine tetrahydrochloride tablets – Orphalan)**
- **Syprine® (trientine hydrochloride capsules – Bausch, generic)**

is(are) considered experimental, investigational, or unproven for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. Biliary Cirrhosis. Trientine is not indicated for the treatment of biliary cirrhosis.¹

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

3. **Rheumatoid Arthritis.** Trientine is not recommended for use in patients with rheumatoid arthritis.¹ Per the prescribing information, trientine was not found to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment in patients with rheumatoid arthritis.
4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Syprine® capsules [prescribing information]. Bridgewater, NJ: Bausch Health; September 2020.
2. Cuvrior™ tablets [prescribing information]. Chicago, IL: Orphalan SA; May 2022.
3. Weiss KH, Thurik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson Disease. *Clin Gastroenterol Hepatol.* 2013;11:1028-1035.
4. Schilsky ML, Roberts EA, et al. A multidisciplinary approach to the diagnosis and management of Wilson's disease: 2022 Practical Guidance on Wilson disease from the AASLD. *Hepatology.* 2023;77(4):1428-1455.
5. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol.* 2012;56(3):671-85.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria change.	11/02/2022
Selected Revision	The title of the policy was updated to add "Products." Cuvrior (trientine tetrahydrochloride tablets) was added to the policy.	05/10/2023
Annual Revision	No criteria change.	11/15/2023

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