BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

**PHARMACY COVERAGE GUIDELINE**

# CUVRIOR™ (trientine tetrahydrochloride) tablet
# SYPRINE® (trientine hydrochloride) capsule
# Trientine Hydrochloride capsule
# Generic Equivalent (if available)

**This Pharmacy Coverage Guideline (PCG):**
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

**Scope**
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid, or members of out-of-state Blue Cross and/or Blue Shield Plans

**Instructions & Guidance**
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

## Criteria:

### SYPRINE (trientine hydrochloride)
### Trientine hydrochloride

➢ **Criteria for initial therapy:** Syprine (trientine hydrochloride) and trientine hydrochloride are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Hepatologist

2. Individual is 6 years of age or older

3. Individual has a confirmed diagnosis of Wilson Disease (hepatolenticular degeneration) due to excess copper

4. Diagnosis of Wilson's Disease is confirmed by **THREE** of the following:
    a. Presence of Kayser-Fleischer rings on slit lamp examination
    b. Low serum ceruloplasmin of less than 20 mg/dL
    c. 24-hour urinary copper is greater than 40 µg/day or greater than 100 µg/day regardless of ceruloplasmin level
    d. **ONE** of the following:
        i. Liver biopsy, if performed, findings are consistent with Wilson Disease
        ii. Ultrasound based transient elastography for fibrosis
    e. Genetic testing findings consistent with Wilson Disease (e.g., biallelic, pathogenic (disease-causing) variants affecting both *ATP7B* alleles)
    f. First degree relative with Wilson Disease

5. Requested agent is for primary removal of copper that has accumulated in tissue in an individual with symptoms consistent with Wilson Disease and/or evidence of organ damage (e.g., neurologic, psychiatric, liver failure, non-immune (Coombs-negative) hemolytic anemia, other)

6. Baseline Leipzig score was 4 or more (see Definitions section)

7. Individual is not simultaneously using trientine hydrochloride (brand Syprine, or generic) with Cuvrior (trientine tetrahydrochloride)

8. **Additional criteria for generic trientine hydrochloride:** Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **penicillamine tablet**

9. **Additional criteria for brand Syprine (trientine hydrochloride):** Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
    a. Penicillamine tablet
    b. Generic trientine hydrochloride

**Initial approval duration**: 6 months

- **Criteria for continuation of coverage (renewal request):** Syprine (trientine hydrochloride) and trientine hydrochloride are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Hepatologist

2. Requested agent is for **ONE** of the following:

a. Primary removal of copper that has accumulated in tissue
b. Transitioning to maintenance/prevention of copper reaccumulating in tissue

3. Individual has documentation of positive clinical response to therapy defined as **ONE** of the following:
   a. For continuation of primary removal of copper: urinary copper excretion increased over baseline
   b. For transitioning to maintenance therapy **ALL** of the following:
      i. There is symptomatic improvement
      ii. Normal or near normal serum aminotransferases and normal hepatic synthetic function
      iii. 24-hour urinary copper excretion is less than 500 mcg/24-hours or less than 100 mcg/24-hours for individual on zinc
      iv. Non-ceruloplasmin bound copper (NCC) is between 25 and 150 microg/L

4. Individual has been adherent with the medication

5. Individual is not simultaneously using trientine hydrochloride (brand Syprine, or generic) with Cuvrior (trientine tetrahydrochloride)

6. **Additional criteria for brand Syprine (trientine hydrochloride):** Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **generic trientine hydrochloride**

**Renewal duration**: 12 months
**Note**: Maintenance therapy options include either a lower dose chelating agent (i.e., reducing the dose by approximately one-third) or zinc

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

## CUVRIOR (trientine tetrahydrochloride)

- **Criteria for initial therapy:** Cuvrior (trientine tetrahydrochloride) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Hepatologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of stable Wilson Disease (hepatolenticular degeneration) due to excess copper who is de-coppered and tolerant to penicillamine

4. Requested agent is for transitioning to maintenance/prevention of copper reaccumulating in tissue in an individual who is de-coppered and tolerant to penicillamine defined as **ALL** of the following:
    a. Individual is adequately controlled and tolerating penicillamine
    b. Non-ceruloplasmin bound copper (NCC) is between 25 and 150 microg/L
    c. 24-hour urinary copper excretion is between greater than or equal to 100 and less than or equal to 900 µg/24 hours
    d. Normal or near normal serum aminotransferases and normal hepatic synthetic function

5. Individual is not simultaneously using Cuvrior (trientine tetrahydrochloride) with trientine hydrochloride (brand Syprine, or generic)

6. **Additional criteria for brand Cuvrior (trientine tetrahydrochloride):** Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
    a. Penicillamine tablet
    b. Generic trientine hydrochloride

7. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

**Initial approval duration**: 6 months

- **Criteria for continuation of coverage (renewal request):** Cuvrior (trientine tetrahydrochloride) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Hepatologist

2. Requested agent is for transitioning to maintenance/prevention of copper reaccumulating in tissue in an individual who is de-coppered and tolerant to penicillamine

3. Individual has documentation of positive clinical response to therapy defined as **ALL** of the following:
    a. Non-ceruloplasmin bound copper (NCC) is between 25 and 150 microg/L
    b. 24-hour urinary copper excretion is between greater than or equal to 100 and less than or equal to 900 µg/24 hours
    c. Normal or near normal serum aminotransferases and normal hepatic synthetic function

4. Individual has been adherent with the medication

5. Individual is not simultaneously using Cuvrior (trientine tetrahydrochloride) with trientine hydrochloride (brand Syprine, or generic)

6. **Additional criteria for brand Cuvrior if available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

**Renewal duration**: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

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**Description:**

Syprine (trientine hydrochloride) capsule and generic trientine hydrochloride capsule are indicated for the treatment of patients with Wilson's disease in those who are intolerant to penicillamine. Trientine is an oral chelating agent structurally dissimilar from penicillamine and other available chelating agents; it is an effective oral chelator of copper used to induce adequate cupriuresis.

Cuvrior (trientine tetrahydrochloride) tablet is indicated for the treatment of adult patients with stable Wilson's disease who are de-coppered and tolerant to penicillamine. Data from a randomized trial suggested that trientine tetrahydrochloride is effective for preventing copper reaccumulation after initial chelation therapy. In an open-label trial including 53 patients with Wilson disease who were initially stabilized with penicillamine, there was no significant differences in serum levels of non-ceruloplasmin-bound copper or in clinical response at 24 and 48 weeks for patients treated with trientine tetrahydrochloride compared with penicillamine. The mean 24-hour urinary copper excretion (UCE) at Week 36 was lower in patients receiving Cuvrior as compared to patients receiving penicillamine. A decrease in UCE has been observed when switching patients from penicillamine products to trientine products. Safety and effectiveness of Cuvrior (trientine tetrahydrochloride) in Wilson's Disease is supported by studies of another trientine product in patients intolerant to penicillamine.

Galzin (zinc acetate) therapy is indicated for maintenance treatment of patients with Wilson's disease who have been initially treated with a chelating agent.

Penicillamine tablet or capsule (DEPEN and generic, Cuprimine and generic), is a chelating agent used in the treatment of Wilson's disease. It is also used to reduce cystine excretion in cystinuria and to treat patients with severe, active rheumatoid arthritis unresponsive to conventional therapy.

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 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.

The pathologic effects seen in Wilson's disease are found in the brain, where degeneration is widespread; in the liver, where fatty infiltration, inflammation, and hepatocellular damage progress to cirrhosis; in the kidney, resulting in tubular and glomerular dysfunction; and in the eye, where characteristic corneal copper deposits are known as Kayser-Fleischer rings.

The majority of patients will die from liver disease (cirrhosis or acute liver failure), the rest die due to complications of progressive neurologic disease.

The diagnosis is suspected on the basis of family or individual history, physical examination, or a low serum concentration of ceruloplasmin. It is confirmed by the demonstration of Kayser-Fleischer rings or, in the asymptomatic patient, by the quantitative demonstration in a liver biopsy specimen of a concentration of copper in excess of 250 mcg/g dry weight.

There are two goals to treatment: (1) minimize dietary intake and absorption of copper; (2) promote excretion of copper deposited in tissues. The first objective is attained by a daily diet that contains no more than 1-2 milligrams of copper. The diet should exclude chocolate, nuts, shellfish, mushrooms, liver, molasses, broccoli, and cereals enriched with copper, and be composed to as great an extent as possible with foods with a low copper content. Distilled or demineralized water should be used if the patient's drinking water contains more than 0.1 mg of copper per liter.

For the second objective, a copper chelating agent is used. In symptomatic patients, this treatment usually produces marked neurologic improvement, a fading of Kayser-Fleischer rings, and a gradual amelioration of hepatic dysfunction and psychic disturbances. Noticeable improvement may not occur for one to three months.

There are two types of patients that require treatment for Wilson's disease: (1) the symptomatic, and (2) the asymptomatic, where the disease will develop in the future if the patient is not treated. Treatment of asymptomatic patients has been conducted for over ten years. Symptoms and signs of the disease appear to be prevented indefinitely if daily treatment can be continued.

A 2023 Practice Guidance on Wilson disease (WD) from the American Association for the Study of Liver Diseases AASLD has the following guidance statements (numbers 15–18). All patients with a newly established diagnosis of WD should be initiated on lifelong medical therapy for WD. Initial treatment for symptomatic patients with WD should include a chelating agent (D-penicillamine or trientine). Treatment of asymptomatic patients with WD can be a chelating agent (D-penicillamine or trientine usually at a lower dose than for initial therapy) or zinc. The suitability for transition to maintenance therapy for WD includes time on therapy (generally more than 1 year) and favorable clinical and biochemical response to therapy. Maintenance therapy may be a lower doses of chelating agent (D-penicillamine or trientine) or full-dose zinc.

Zinc may be used in patients who are reluctant to use a chelating agent or who become intolerant. Liver test should be monitored at least every four months and a chelating agent added if these tests worsen. Maintenance therapy can be achieved with zinc or with lower doses of a chelator. Zinc acetate is usually not used for the initial therapy of symptomatic patients because of the time required for zinc-induced increase in enterocytic metallothionein and blockade of copper uptake.

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# CUVRIOR™ (trientine tetrahydrochloride) tablet
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**Definitions:**

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

**Liver biopsy** — For patients with inconclusive initial testing who undergo a liver biopsy, determine hepatic copper concentration:

- A diagnosis of Wilson disease is established if the hepatic copper concentration is >250mcg/g dry weight (4 micromol/g dry weight)
- A diagnosis of Wilson disease is excluded if the hepatic copper concentration is <50 mcg/gdry weight (0.8 micromol/g dry weight)
- Histologic findings may include fatty infiltration within hepatocytes, glycogen inclusions within nuclei, and portal fibrosis

**Leipzig scoring system for diagnosis of Wilson's Disease**

| Typical Clinical Signs and Symptoms | Allocated Score Per Item |
|---|---|
| Kayser-Fleischer rings | |
| Present | 2 |
| Absent | 0 |
| Neurologic* | |
| Severe | 2 |
| Mild | 1 |
| Absent | 0 |
| Serum ceruloplasmin | |
| Normal (> 0.2 g/L) | 0 |
| 0.1 to 0.2 g/L | 1 |
| < 0.1 g/L | 2 |
| Coombs-negative (non-immune) hemolytic anemia | |
| Present | 1 |
| Absent | 0 |
| **Other Tests** | |
| Liver copper (in the absence of cholestasis) | |
| > 5 times ULN (> 4 µmol/g) | 2 |
| 0.8 to 4 µmol/g | 1 |
| Normal (< 0.8 µmol/g) | -1 |
| Rhodanine-positive granules** | 1 |
| Urinary copper (in the absence of acute hepatitis) | |
| Normal | 0 |
| 1 to 2 times ULN | 1 |
| >2 times ULN | 2 |
| Normal, but 5 times ULN after penicillamine | 2 |

| | |
|---|---|
| Mutation analysis *ATP7B* gene, on chromosome 13<br>On both chromosomes detected<br>On 1 chromosome detected<br>No mutations detected | <br>4<br>1<br>0 |
| **Evaluation based on Total Leipzig Score** | |
| **Total Score** | **Evaluation** |
| ≥ 4 | Diagnosis established |
| 3 | Diagnosis possible, more tests needed |
| ≤ 2 | Diagnosis very unlikely |
| * Motor disorders (ataxia, tremors, speech difficulties, dysarthria, dystonia, risus sardonicus) and psychiatric manifestations (irritability, depression, deterioration of work performance) or typical abnormalities at brain magnetic resonance imaging<br>** If no quantitative liver copper available | |

**AASLD 2023 Practice Guidance on Wilson disease (WD):**

Guidance statements 15–18

15. All patients with a newly established diagnosis of WD should be initiated on lifelong medical therapy for WD.

16. Initial treatment for **symptomatic** patients with WD should include a chelating agent (D-penicillamine or trientine).

17. Treatment of **asymptomatic** patients with WD can be with a chelating agent (D-penicillamine or trientine at a lower dose than for initial therapy) or with zinc.

18. The suitability for transition to maintenance therapy for WD includes time on therapy (generally more than 1 year) and favorable clinical and biochemical response to therapy. **Maintenance therapy** may be a lower dose of chelating agent (D-penicillamine or trientine) or full-dose zinc.

**Resources:**

Cuvrior (trientine tetrahydrochloride) tablet product information, revised by Orphalan SA. 04-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Syprine (trientine hydrochloride) capsule product information, revised by Bausch Health US LLC 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Trientine hydrochloride capsule product information, revised by Accord Healthcare, Inc. 08-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Schilsky ML. Wilson disease: Management. In: UpToDate, Rand EB, Robson KM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated January 028, 2025. Accessed June 23, 2025.

Schilsky ML. Wilson disease: Clinical manifestations, diagnosis, and natural history. In: UpToDate, Rand EB, Aminoff MJ, Robson KM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated June 05, 2025. Accessed June 23, 2025.

Schilsky ML, Roberts EA, Bronstein JM, et al.: A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. Hepatology 2023 https://doi.org/10.1002/hep.32801. Accessed May 23, 2023. Re-evaluated June 23, 2025.

Schilsky ML, Czlonkowska A, Zuin M, et al: Trientine tetrahydrochloride versus penicillamine for maintenance therapy in Wilson disease (CHELATE): a randomized, open-label, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol 2022 December; 7: 1092–1102. Accessed May 08, 2023. Re-evaluated June 23, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03539952: CHELATE STUDY: Trientine Tetrahydrochloride (TETA 4HCL) for the Treatment of Wilson's Disease. Available from: http://clinicaltrials.gov. Last update posted April 20, 2023. Last verified February 2023. Accessed May 08, 2023. Re-evaluated June 23, 2025.