Effective Date **3/15/2025**
Coverage Policy Number **IP0278**

Trientine Products

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following trientine products:

- **Cuvrior™** (trientine tetrahydrochloride tablets)
- **Syprine®** (trientine hydrochloride capsules)
- **trientine hydrochloride**

Medical Necessity Criteria

Trientine Products (Cuvrior, Syprine, and generics) are considered medically necessary when the following are met:

1. **Wilson's Disease.** Individual meets **ALL** of the following criteria:
    A. Diagnosis of Wilson's disease confirmed by documentation of **ONE** of the following:
        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. Documentation of **ONE** of the following criteria:
        i. Failure, contraindication or intolerance to penicillamine therapy (Cuprimine®, Depen®, or generics)
        ii. Has neurologic manifestations of Wilson's disease
        iii. Individual is pregnant
        iv. Has been started on therapy with trientine (Cuvrior or Syprine)
    C. The medication is prescribed by, or in consultation with, a gastroenterologist, hepatologist, or liver transplant physician
    D. Preferred Product Criteria is met, refer to below table(s)

For Employer Plans:

Product	Criteria
Cuvrior (trientine tetrahydrochloride)	Documentation of failure, contraindication, or intolerance to trientine hydrochloride [may require prior authorization]
Syprine (trientine hydrochloride)	Documented trial of **trientine hydrochloride** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction [may require prior authorization]

For Individual and Family Plans:

Product	Criteria
Cuvrior (trientine tetrahydrochloride)	Documentation of failure, contraindication, or intolerance to penicillamine 250mg tablets [may require prior authorization]
Syprine (trientine hydrochloride)	Documentation of failure, contraindication, or intolerance to penicillamine 250mg tablets [may require prior authorization]
trientine hydrochloride 250mg, 500mg capsules	Documentation of failure, contraindication, or intolerance to penicillamine 250mg tablets [may require prior authorization]

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.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of trientine products is considered medically necessary for **ALL** covered diagnosis when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

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

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

2. **Cystinuria.**
   Trientine 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 is not recommended for use in individuals 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 of individuals with rheumatoid arthritis .

Background

OVERVIEW
Trientine products (capsules [Syprine, generic] 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:[1]
- Treatment of patients with **Wilson's disease** who are intolerant of penicillamine.

Cuvrior (trientine tetrahydrochloride tablets) is indicated for:[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 array 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.

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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	No criteria changes	3/15/2025

The policy effective date is in force until updated or retired.