Pharmacy Policy Bulletin: J-0484 Trientine and Penicillamine Products – Commercial and Healthcare Reform	
Number: J-0484	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0484-014	**Original Date:** 07/21/2016
Effective Date: 07/18/2025	**Review Date:** 06/25/2025

Drugs Product(s):	• Cuprimine (penicillamine) capsule • Cuvrior (trientine tetrahydrochloride) • Depen (penicillamine) tablet • Syprine (trientine hydrochloride) • Trientine hydrochloride

FDA-Approved Indication(s):	• **Cuprimine (penicillamine) capsule, Depen (penicillamine) tablet**
	  ○ Treatment of Wilson's disease
	  ○ Treatment of cystinuria
	  ○ Treatment of severe, active rheumatoid arthritis (RA) that has failed to respond to an adequate trial of conventional therapy
	• **Cuvrior (trientine tetrahydrochloride)**
	  ○ Treatment of adult patients with stable Wilson's disease who are de-coppered and tolerant to penicillamine
	• **Syprine (trientine hydrochloride) or trientine hydrochloride**
	  ○ Treatment of Wilson's disease in patients who are intolerant of penicillamine

Background:	• Penicillamine and trientine hydrochloride are oral chelating agents that promote copper excretion, the action responsible for their effectiveness in Wilson's disease. • According to the American Association for the Study of Liver Diseases (AASLD) guidelines, treatment of Wilson's disease for symptomatic patients should include a chelating agent. • Wilson's disease is treated with pharmacologic chelators in two phases, the first phase removing existing copper that has accumulated (specifically de-coppering) and the second phase focusing on preventing further accumulation. The main chelator used in the treatment of Wilson's disease is penicillamine. Trientine can also be used and is associated with a lower incidence of side effects. Use of zinc can also prevent reaccumulation of copper, but is not

preferred for initial removal of existing copper. Initial treatment for symptomatic patients includes a chelating agent (penicillamine or trientine).

- AASLD guidelines state that treatment of pre-symptomatic patients or those on maintenance therapy can be accomplished with a chelating agent or zinc.
- AASLD guidelines state that trientine may be better tolerated. The guidelines state that neurological worsening occurred more frequently with penicillamine than with trientine. Severe side effects require penicillamine to be discontinued in roughly 30% of patients.
- D-penamine is not FDA-approved, but the FDA temporarily allowed its use for Depen indications due to a now-resolved shortage of that product.
- Prescribing Considerations:
    - Trientine and penicillamine should be given on an empty stomach, at least one hour before meals or two hours after meals, and at least one hour apart from any other drug, food, or milk.
    - Generally, dosages up to 500 mg/day can be given as a single daily dose. Dosages in excess of 500 mg/day should be administered in divided doses.
    - **Penicillamine**
        - Penicillamine should not be used in patients receiving concurrent gold therapy, antimalarial or cytotoxic drugs, oxyphenbutazone, or phenylbutazone because they are associated with similar serious hematologic and renal adverse reactions.
        - Patients allergic to penicillin may theoretically have cross-sensitivity to penicillamine, but there is no risk of contamination of penicillamine by penicillin because of the synthetic manufacturing process.
        - Liver function tests are recommended when taking penicillamine. Intervals vary by place in therapy and indication.
        - Because of the potential for serious hematological and renal adverse reactions with penicillamine, routine urinalysis, white and differential blood cell count, hemoglobin determination, and direct platelet count should be completed along with monitoring of patient's skin, lymph node, and body temperature.
        - Wilson's Disease: Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum.
        - Cystinuria: It is recommended to be used along with conventional therapy.
        - Rheumatoid Arthritis: The onset of therapeutic response is typically delayed. Two or three months may be required before the first evidence of a clinical response is note. If the patient has been in remission for six months or more, a gradual, stepwise dosage reduction at approximately three-month intervals may be attempted.
    - **Trientine**
        - Adjust trientine dosage according to clinical assessment and laboratory monitoring of copper. Adjust the total daily dosage according to clinical assessment and serum non-ceruloplasmin copper (NCC) levels. Evaluate serum NCC levels when initiating treatment, after 3 months of treatment and approximately every 6 months thereafter. Therapy may also be monitored periodically (every 6 to 12 months) with measurement of 24-hour urinary copper excretion (UCE).

	Optimal long-term maintenance dosage should be determined at 6-to-12-month intervals. ▪ Patients, especially women, taking trientine should be monitored for iron deficiency anemia. ▪ Patients taking trientine should take their temperature nightly for the first month of treatment and report any fever or skin eruption. ▪ Unlike penicillamine, trientine is not recommended in cystinuria or rheumatoid arthritis as trientine was reported not to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment.

Approval Criteria

I. Cuprimine (penicillamine) capsule

A. Initial Authorization

1. Wilson's disease

When a benefit, coverage of Cuprimine (penicillamine) capsule may be approved when all of the following criteria are met **(a. and b.)**:

a. The member has a diagnosis of Wilson's disease (ICD-10: E83.01).

b. If the request is for brand Cuprimine, the member has experienced therapeutic failure or intolerance to all the following products **(i. and ii.)**:

i. generic penicillamine capsule

ii. plan-preferred generic penicillamine tablet

2. Cystinuria

When a benefit, coverage of Cuprimine (penicillamine) capsule may be approved when all of the following criteria are met **(a. and b.)**:

a. The member has a diagnosis of cystinuria (ICD-10: E72.01).

b. If the request is for brand Cuprimine, the member has experienced therapeutic failure or intolerance to all the following products **(i. and ii.)**:

i. generic penicillamine capsule

ii. plan-preferred generic penicillamine tablet

3. Rheumatoid Arthritis

When a benefit, coverage of Cuprimine (penicillamine) capsule may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member has a diagnosis of RA (ICD-10: M05 and M06).

b. The member has experienced therapeutic failure or intolerance to two (2) nonbiologic DMARDs, or contraindication to all (for example methotrexate, leflunomide, sulfasalazine, hydroxychloroquine).

c. If the request is for brand Cuprimine, the member has experienced therapeutic failure or intolerance to all the following products **(i. and ii.)**:

i. generic penicillamine capsule

ii. plan-preferred generic penicillamine tablet

B. Reauthorization

1. Wilson's disease, Cystinuria, or Rheumatoid Arthritis

When a benefit, coverage of Cuprimine (penicillamine) capsule may be approved when all of the following criteria are met **(a. and b.)**:

a. The prescriber attests that the member has experienced positive clinical response to therapy.
b. If the request is for brand Cuprimine, the member has experienced therapeutic failure or intolerance to all the following products **(i. and ii.)**:
i. generic penicillamine capsule
ii. plan-preferred generic penicillamine tablet

II. Depen (penicillamine) tablet

A. Initial Authorization

1. Wilson's disease
When a benefit, coverage of Depen (penicillamine) tablet may be approved when all of the following criteria are met **(a., b., and c.)**:
a. The member has a diagnosis of Wilson's disease (ICD-10: E83.01).
b. The member has experienced therapeutic failure or intolerance to plan-preferred generic penicillamine capsule.
c. If the request is for brand Depen, the member has experienced therapeutic failure or intolerance to generic penicillamine tablet.

2. Cystinuria
When a benefit, coverage of Depen (penicillamine) tablet may be approved when all of the following criteria are met **(a., b., and c.)**:
a. The member has a diagnosis of cystinuria (ICD-10: E72.01).
b. The member has experienced therapeutic failure or intolerance to plan-preferred generic penicillamine capsule.
c. If the request is for brand Depen, the member has experienced therapeutic failure or intolerance to generic penicillamine tablet.

3. Rheumatoid Arthritis
When a benefit, coverage of Depen (penicillamine) tablet may be approved when all of the following criteria are met **(a. through d.)**:
a. The member has a diagnosis of RA (ICD-10: M05 and M06).
b. The member has experienced therapeutic failure or intolerance to two (2) nonbiologic DMARDs, or contraindication to all (for example methotrexate, leflunomide, sulfasalazine, hydroxychloroquine).
c. The member has experienced therapeutic failure or intolerance to plan-preferred generic penicillamine capsule.
d. If the request is for brand Depen, the member has experienced therapeutic failure or intolerance to generic penicillamine tablet.

B. Reauthorization

1. Wilson's disease, Cystinuria, or Rheumatoid Arthritis
When a benefit, coverage of Depen (penicillamine) tablet may be approved when all of the following criteria are met **(a., b., and c.)**:
a. The prescriber attests that the member has experienced positive clinical response to therapy.
b. The member has experienced therapeutic failure or intolerance to plan-preferred generic penicillamine capsule.
c. If the request is for brand Depen, the member has experienced therapeutic failure or intolerance to generic penicillamine tablet.

III. Cuvrior

A. Initial Authorization

1. Wilson's disease

When a benefit, coverage of Cuvrior may be approved when all of the following criteria are met **(a. through d.)**:

- **a.** The member is 18 years of age or older.
- **b.** The member has a diagnosis of Wilson's disease (ICD-10: E83.01), classified as stable.
- **c.** The member has previously tolerated one (1) penicillamine product used for de-coppering (for example generic penicillamine capsule or tablet, Depen)
- **d.** The member has experienced therapeutic failure or intolerance to plan-preferred generic trientine hydrochloride.

B. Reauthorization

1. Wilson's disease

When a benefit, coverage of Cuvrior may be approved when all of the following criteria are met **(a. and b.)**:

- **a.** The prescriber attests that the member has experienced positive clinical response to therapy.
- **b.** The member has experienced therapeutic failure or intolerance to plan-preferred generic trientine hydrochloride.

IV. Syprine (trientine hydrochloride) or trientine hydrochloride

A. Initial Authorization

1. Wilson's disease

When a benefit, coverage of Syprine (trientine hydrochloride) or trientine hydrochloride may be approved when all of the following criteria are met **(a. through d.)**:

- **a.** The member has a diagnosis of Wilson's disease (ICD-10: E83.01).
- **b.** The member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred generic penicillamine capsule.
- **c.** If the request is for brand Syprine, the member has experienced therapeutic failure or intolerance to generic trientine hydrochloride 250 mg capsules.
- **d.** If the request is for trientine hydrochloride 500 mg capsules, the member has experienced therapeutic failure or intolerance to plan-preferred generic trientine hydrochloride 250 mg capsules.

B. Reauthorization

2. Wilson's disease

When a benefit, coverage of Syprine (trientine hydrochloride) or trientine hydrochloride may be approved when all of the following criteria are met **(a. through d.)**:

- **a.** The prescriber attests that the member has experienced positive clinical response to therapy.
- **b.** The member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred generic penicillamine capsule.
- **c.** If the request is for brand Syprine, the member has experienced therapeutic failure or intolerance to generic trientine hydrochloride 250 mg capsules.

d. If the request is for trientine hydrochloride 500 mg capsules, the member has experienced therapeutic failure or intolerance to plan-preferred generic trientine hydrochloride 250 mg capsules.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Cuprimine [package insert]. Bridgewater, NJ: Bausch Health US, LLC; October 2020.
2. Cuvrior [package insert]. Chicago, IL: Orphalan SA; April 202.
3. Depen [package insert]. Canonsburg, PA: Meda Pharmaceuticals Inc.; July 2023.
4. Syprine [package insert]. Bridgewater, NJ: Bausch Health US, LLC; November 2020.
5. Trientine hydrochloride [package insert]. Durham, NC: Accord Healthcare, Inc.; May 2019.
6. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guidelines for the treatment of Rheumatoid Arthritis. *Arthritis Care & Research.* 2021;73(7):924-939.
7. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: An update. *Hepatology*. 2008;47(6):2089-2111.
8. U.S. Food & Drug Administration. Temporary importation of D-penamine (D-penicillamine) 125 mg tablets to address shortage. Available at: https://www.fda.gov/media/119423/download. Accessed January 13, 2022.
9. 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*.