Drug and Biologic Coverage Policy

Effective Date..... 5/1/2025
Coverage Policy Number.....IP0277

Penicillamine

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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

Penicillamine products (capsules [Cuprimine, generic] and tablets [Depen, generic]) are chelating agents indicated for the following uses:[1,2]

- **Cystinuria**.
- **Rheumatoid arthritis**, severe, active disease in patients who have failed to respond to an adequate trial of conventional therapy.
- **Wilson's disease** (hepatolenticular degeneration).

Product labeling for Cuprimine and Depen is identical, apart from the differences in dosage forms: Cuprimine is supplied as 250 mg capsules; Depen is supplied as 250 mg tablets.[1,2]

Guidelines
Penicillamine is discussed in the following guidelines:

- **Rheumatoid Arthritis:** Guidelines from American College of Rheumatology (2021) do not provide recommendations specifically for the use of penicillamine for rheumatoid arthritis.[5]
- **Wilson's Disease:**
  The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2022).[3] 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 levels < 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 in 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).[4] 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.

Medical Necessity Criteria

Penicillamine products (Cuprimine, Depen, and generics) are considered medically necessary when ONE of the following is 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:
      i. Failure, contraindication, or intolerance to zinc acetate capsules (Galzin®) or another zinc product (for example zinc sulfate, zinc gluconate)
      ii. According to the prescriber, the individual has <u>symptomatic</u> Wilson's disease and zinc would not be an appropriate therapy
      iii. Has been started on therapy with a penicillamine product
   C. The medication is prescribed by, or in consultation with, a gastroenterologist, hepatologist, or liver transplant physician
   D. Preferred product criteria are met for the product(s) as listed in the below table(s)

2. **Cystinuria.** Individual meets **BOTH** of the following criteria:
   A. Documented failure or inability to adhere to increased fluid intake, restriction of sodium and protein intake, and urinary alkalinization
   B. Preferred product criteria are met for the product(s) as listed in the below table

3. **Lead Poisoning.** Individual meets **ALL** of the following criteria:
    A. Documentation of a blood lead level greater than 44 µg/dL
    B. Documentation of failure, contraindication, or intolerance **BOTH** of the following:
        i. succimer (Chemet®)
        ii. edetate calcium disodium (Calcium Disodium Versenate)
    C. Preferred product criteria are met for the product(s) as listed in the below table(s)

Employer Plans:

Product	Criteria
Cuprimine (penicillamine capsules)	Documented trial of **penicillamine capsules** (the bioequivalent 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]
Depen (penicillamine tablets)	Documented trial of **penicillamine capsules** (the bioequivalent 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]

Individual and Family Plans:

Product	Criteria
Cuprimine (penicillamine capsules)	Documentation of failure, contraindication, or intolerance to penicillamine tablets [prior authorization required]
Depen (penicillamine tablets)	Documentation of failure, contraindication, or intolerance to penicillamine tablets [prior authorization required]
Penicillamine 250mg capsules	Documentation of failure, contraindication, or intolerance to penicillamine tablets [prior authorization required]

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 penicillamine 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.

References

1. Cuprimine® capsules [prescribing information]. Bridgewater, NJ. Valeant; November 2019.
2. Depen® tablets [prescribing information]. Somerset, NJ. Meda; January 2019.
3. 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.
4. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol.* 2012;56(3):671-85.
5. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2021 Jul;73(7):924-939.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	3/15/2025
Annual Revision	No criteria changes.	5/1/2025

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