PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Penicillamine Products Prior Authorization with Step Therapy Policy
- Cuprimine® (penicillamine capsules – Valeant, generic)
- Depen® (penicillamine tablets – Meda, generic)

REVIEW DATE: 03/18/2026; selected revision 04/01/2026

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 WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Penicillamine products (capsules [Cuprimine, generic] and tablets [Depen, generic]), disease modifying antirheumatic drugs, 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).

The product labeling for Cuprimine and Depen are 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* variants 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) and the European Reference Network (ERN) published updated clinical practice guidelines for Wilson's disease (2025).[4] These guidelines indicate ceruloplasmin and 24-h urinary copper excretion remain the most common tests used for the diagnosis of Wilson's disease. Diagnosis should be based on a combination of clinical features, biochemical tests (including serum ceruloplasmin, 24-hour urinary copper excretion, and hepatic copper content), and molecular analysis of *ATP7B*. The Leipzig score is also mentioned, and updated guidelines added relative exchangeable copper (REC) as an additional diagnostic marker when available. The EASL/ERN recommend chelating agents (penicillamine or trientine) as first-line therapy option for patients with significant liver disease. Either chelators or zinc salts may be used for patients with neurological presentations or for maintenance therapy.

Safety

The penicillamine products labeling has a Boxed Warning advising physicians planning to use penicillamine should thoroughly familiarize themselves with its toxicity, special dosage considerations, and therapeutic benefits.[1] Penicillamine should never be used casually. Each patient should remain constantly under the close supervision of the physician. Patients should be warned to report promptly any symptoms suggesting toxicity. The use of penicillamine has been associated with fatalities due to certain diseases, such as aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome, and myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the penicillamine products. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, the patient is directed to try generic penicillamine (Step 1) prior to brand Cuprimine or Depen (Step 2). If the patient is requesting brand Cuprimine or brand Depen and meets the standard *Chelating Agents*

– *Penicillamine Prior Authorization* criteria, but has not met the Step Therapy requirement (i.e., has not tried generic penicillamine), an approval for generic penicillamine will be authorized. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with penicillamine products for Wilson's disease as well as the monitoring required for adverse events and long-term efficacy, approval for this condition requires penicillamine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

I. Penicillamine capsules (Cuprimine, 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 Indications

1. **Cystinuria.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** According to the prescriber, patient has tried increased fluid intake; restriction of sodium and protein; and urinary alkalinization; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine capsules are requested; OR
     - **ii.** If brand Cuprimine is being requested, patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Wilson's Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Diagnosis of Wilson's disease is confirmed by ONE of the following (i or ii):
     - **i.** Genetic testing results confirming biallelic pathogenic *ATP7B* variants (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; OR
       - **b)** Serum ceruloplasmin level < 20 mg/dL; OR
       - **c)** Liver biopsy findings consistent with Wilson's disease; OR
       - **d)** 24-hour urinary copper > 40 mcg/24 hours; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried Galzin (zinc acetate capsules); OR
     - **ii.** Patient has tried another zinc product (e.g., zinc sulfate, zinc gluconate, zinc acetate); OR
     - **iii.** According to the prescriber, patient has symptoms of Wilson's disease and zinc would not be an appropriate therapy; OR
     - **iv.** Patient has been started on therapy with a penicillamine product; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine capsules are requested; OR

ii. If brand Cuprimine is being requested, patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction; AND

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

II. Penicillamine tablets (Depen, 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 Indications

1. **Cystinuria.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** According to the prescriber, patient has tried increased fluid intake; restriction of sodium and protein; and urinary alkalinization; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine tablets are requested; OR
     - **ii.** If brand Depen is being requested, patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Wilson's Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Diagnosis of Wilson's disease is confirmed by ONE of the following (i or ii):
     - **i.** Genetic testing results confirming biallelic pathogenic *ATP7B* variants (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; OR
       - **b)** Serum ceruloplasmin level < 20 mg/dL; OR
       - **c)** Liver biopsy findings consistent with Wilson's disease; OR
       - **d)** 24-hour urinary copper > 40 mcg/24 hours; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried Galzin (zinc acetate capsules); OR
     - **ii.** Patient has tried another zinc product (e.g., zinc sulfate, zinc gluconate, zinc acetate); OR
     - **iii.** According to the prescriber, patient has symptoms of Wilson's disease and zinc would not be an appropriate therapy; OR
     - **iv.** Patient has been started on therapy with a penicillamine product; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine tablets are requested; OR

ii. If brand Depen is being requested, patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction; AND

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

CONDITIONS NOT COVERED

- **Cuprimine® (penicillamine capsules – Valeant, generic)**
- **Depen® (penicillamine tablets – Meda, generic)**

is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available.

REFERENCES

1. Cuprimine® capsules [prescribing information]. Bridgewater, NJ. Valeant; January 2026.
2. Depen® tablets [prescribing information]. Somerset, NJ. Meda; July 2023.
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 the Study of the Liver (EASL); European Reference Network (ERN). EASL-ERN Clinical Practice Guidelines on Wilson's disease. *J Hepatol*. 2025;82(4):690-728.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Title** was updated to add "with Step Therapy."	11/15/2023
Annual Revision	No criteria changes.	12/11/2024
Early Annual Revision	**Policy Statement** was updated to add "This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, the patient is directed to try generic penicillamine (Step 1) prior to brand Cuprimine or Depen (Step 2). If the patient is requesting brand Cuprimine or brand Depen and meets the standard *Chelating Agents – Penicillamine Prior Authorization* criteria, but has not met the Step Therapy requirement (i.e., has not tried generic penicillamine), an approval for generic penicillamine will be authorized." Throughout the Policy, the requirement for if Brand name being "prescribed" was reworded to "requested."	03/19/2025
Annual Revision	No criteria changes.	03/18/2026
Selected Revision	Throughout the Policy, the term "mutation(s)" was updated to "variant(s)."	04/01/2026