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: 03/19/2025

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.

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of penicillamine capsules (Cuprimine, generic) is recommended in those who meet one of the following criteria:

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* mutations (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. Coverage of penicillamine tablets (Depen, generic) is recommended in those who meet one of the following criteria:

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* mutations (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.

Coverage of penicillamine products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cuprimine® capsules [prescribing information]. Bridgewater, NJ. Valeant; November 2019.
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 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.