PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 04/07/2021

OVERVIEW

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

- **Wilson's disease**.
- **Cystinuria**.
- **Severe, active rheumatoid arthritis**, in patients who have failed to respond to an adequate trial of conventional therapy.

Product labeling for Cuprimine and Depen is identical, with the exception of the differences in dosage forms; Cuprimine is supplied as 250 mg capsules; Depen is supplied as 250 mg tablets.[1-2]

Wilson's Disease Overview

Wilson's disease is an inherited 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 eventually is released into the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea). 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, penicillamine acts as a general metal chelator and promotes urinary copper excretion.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2008).[4] The AASLD recommends that initial treatment for symptomatic patients include a chelating agent (penicillamine or trientine). 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 again, 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.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of the penicillamine products. All approvals are provided for the duration listed below. Because of the specialized skills required for evaluation and diagnosis of patients treated with penicillamine products as well as the monitoring required for adverse events and long-term efficacy, approval 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
Coverage of the penicillamine products is recommended in those who meet the following criteria:

I. Coverage of Cuprimine and penicillamine capsules is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Wilson's Disease.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** Patient meets ONE of the following criteria (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
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine capsules are requested; OR
     - **ii.** If brand Cuprimine is prescribed, 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
   - **C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

2. **Cystinuria.** Approve for 3 years if the patient meets ONE of the following criteria (A or B):
   - **A)** Generic penicillamine capsules are requested; OR
   - **B)** If brand Cuprimine is prescribed, 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.

3. **Rheumatoid Arthritis.** Approve for 3 years if the patient meets ONE of the following criteria (A or B):
   - **A)** Generic penicillamine capsules are requested; OR
   - **B)** If brand Cuprimine is prescribed, 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.

II. Coverage of Depen and penicillamine tablets is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Wilson's Disease.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** Patient meets ONE of the following criteria (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
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine tablets are requested; OR
     - **ii.** If brand Depen is prescribed, 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
   - **C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

2. **Cystinuria.** Approve for 3 years if the patient meets ONE of the following criteria (A or B):
   - **A)** Generic penicillamine tablets are requested; OR
   - **B)** If brand Depen is prescribed, 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.

3. **Rheumatoid Arthritis.** Approve for 3 years if the patient meets ONE of the following criteria (A or B):
   - **A)** Generic penicillamine tablets are requested; OR
   - **B)** If brand Depen is prescribed, 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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® [prescribing information]. Bridgewater, NJ. Aton Pharma. Inc., a division of Valeant Pharmaceuticals North America LLC; November 2019.
2. Depen® [prescribing information]. Somerset, NJ. Meda Pharmaceuticals Inc.; January 2019.
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. Roberts EA, Schilsky MI. AASLD Practice Guidelines: Diagnosis and treatment of Wilson Disease: an update. *Hepatology*. 2008;47(6):2089-2111.
5. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-85.