Clinical Policy: Penicillamine (Cuprimine)

Reference Number: CP.PCH.09
Effective Date: 12.01.18
Last Review Date: 11.22
Line of Business: Commercial, HIM

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Penicillamine (Cuprimine®) is a chelating agent.

FDA Approved Indication(s)

Cuprimine is indicated for the treatment of:

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

Limitation(s) of use: Available evidence suggests that Cuprimine is not of value in ankylosing spondylitis.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Cuprimine is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Wilson's Disease (must meet all)**:**

1. Diagnosis of Wilson's disease;
2. Member must use generic Depen®, unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 2 g (8 capsules) per day.

Approval duration:
HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Cystinuria (must meet all)**:**

1. Diagnosis of cystinuria;
2. Failure of a urinary alkalinizing agent (e.g., potassium citrate) unless contraindicated or clinically significant adverse effects are experienced;
3. Member must use generic Depen®, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 4 g (16 capsules) per day.

Approval duration:
HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

C. Rheumatoid Arthritis (must meet all)**:**
1. Diagnosis of RA;
2. Member meets one of the following (a or b):
   a. Failure of ≥ 3 consecutive months of methotrexate;
   b. If intolerance or contraindication to methotrexate, failure of ≥ 3 consecutive months of sulfasalazine, leflunomide, or hydroxychloroquine unless contraindicated or clinically significant adverse effects are experienced;
3. Member must use generic Depen®, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed:
   a. Initial therapy: 250 mg (1 capsule) per day for at least the first month;
   b. Maintenance therapy: 1.5 g (6 capsules) per day.

Approval duration:
HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.33 for health insurance marketplace; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and HIM.PA.154 for health insurance marketplace.

II. Continued Therapy

A. All Indications in Section 1 (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed (a, b, or c):
   a. Wilson's disease: 2 g (8 capsules per day) per day;
   b. RA: 1.5 g per day (6 capsules per day);
   c. Cystinuria: 4 g (16 capsules) per day.

Approval duration:
HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.33 for health insurance marketplace; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and HIM.PA.154 for health insurance marketplace.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial and HIM.PA.154 for health insurance marketplace, or evidence of coverage documents;
B. Ankylosing spondylitis.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
RA: rheumatoid arthritis

Appendix B: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
penicillamine (Depen®)	Wilson's disease 250 mg PO QID; adjust to achieve urinary copper excretion 0.5-1 mg/day	Wilson's disease: 2 g/day (750 mg/day if pregnant)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Cystinuria 250 mg PO QD; increase gradually to 1-2 g/day in 4 divided doses and adjust to achieve target urinary cysteine excretion RA 125-250 mg PO QD; increase at 1-3 month intervals by 125-250 mg/day according to response and tolerance (typical maintenance range: 500-750 mg/day) – if no improvement at 1-1.5 g/day after 3-4 months, therapy should be discontinued as a response is unlikely to occur	Cystinuria: 5 g/day RA: 1.5 g/day
potassium citrate	Cystinuria* 60-80 mEq/day divided into 3-4 doses (15–20 mL/day); titrate to achieve a urine pH within target range 7-7.5	See regimen
methotrexate (Rheumatrex®)	RA 7.5 mg/week PO, SC, or IM or 2.5 mg PO Q12 hr for 3 doses/week	30 mg/week
sulfasalazine (Azulfidine®)	RA 2 g/day PO in divided doses	3 g/day
leflunomide (Arava®)	RA 100 mg PO QD for 3 days, then 20 mg PO QD	20 mg/day
hydroxychloroquine (Plaquenil®)	RA* Initial dose: 400 – 600 mg/day PO QD Maintenance dose: 200 – 400 mg/day PO QD	600 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of penicillamine-related aplastic anemia or agranulocytosis, nursing, patients with RA and cystinuria who are pregnant (exceptions can be made for certain patients with cystinuria), patients with RA and history or other evidence of renal insufficiency.
- Boxed warning(s): none reported

Appendix D: General Information

- Although the prescribing information for Cuprimine does not include an absolute maximum dose for Wilson's disease, it notes it is seldom necessary to exceed a dose of 2 g/day. In addition, both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver do not recommend doses higher than 1.5 g/day due to potential for rapid and often irreversible neurological deterioration.
- In cystinuria, initial therapy includes high fluid intake, sodium and protein restriction, and urinary alkalinization. The preferred agent for urinary alkalinization is potassium citrate. Other agents that can be used include potassium bicarbonate, acetazolamide, and sodium bicarbonate or citrate.
- In RA, failure of methotrexate or disease-modifying antirheumatic drugs is defined as ≤ 50% decrease in swollen joint count, ≤ 50% decrease in tender joint count, and ≤ 50% decrease in erythrocyte sedimentation rate (ESR), or ≤ 50% decrease in C-reactive protein (CRP).
- Examples of positive response include: Wilson's disease: reduction in 24-hour urinary copper excretion; cystinuria: reduction in urinary cysteine level; RA: improvement in symptoms.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Cystinuria	1-4 g/day PO in 4 divided doses	4 g/day
Wilson's disease	750-1,500 mg/day PO in divided doses	2 g/day
RA	125-250 mg PO QD	1.5 g/day

VI. Product Availability

Capsule: 250 mg

VII. References

1. Cuprimine Prescribing Information. Bridgewater, NJ: Aton Pharma, Inc.; October 2004. Available at: www.fda.gov. Accessed June 23, 2022.
2. Roberts EA and Schilsky ML. AASLD practice guidelines: Diagnosis and treatment of Wilson disease: an update. Hepatol. 2008; 47(6): 2089-2111.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: Wilson's disease. J Hepatol. 2012; 56(3): 671-685.
4. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. Published 2014. Available at: http://www.auanet.org/guidelines/medical-management-of-kidney-stones-(2014).
5. Goldstein R, Goldfarb DS. Early recognition and management of rare kidney stone disorders. Urol Nurs. 2017 Mar-Apr; 37(2): 81–102.
6. Biyani CS and Cartledge JJ. Cystinuria–diagnosis and management. EAU-EEU Update Series 4. 2006: 175-183.
7. Singh HA, Saag KG, Bridges SL Jr., et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care & Research. 2015; 68: 1-25.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved corporate policies HIM.PA.142 and CP.CPA.312; no significant changes from previously approved corporate policy; commercial: cystinuria – added requirement for trial of a first-line urinary alkalinizing agent, RA – added requirement for trial of a first-line DMARD; references reviewed and updated.	08.07.18	11.18
4Q 2019 annual review: no significant changes; removal of double negative adverse effects and contraindications from RA criteria; references reviewed and updated.	08.15.19	11.19
4Q 2020 annual review: no significant changes; references reviewed and updated.	08.11.20	11.20
Clarify redirection is to generic Depen, modify redirect language to state "Member must use generic Depen".	06.02.21	
4Q 2021 annual review: no significant changes; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	08.27.21	11.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	09.27.21	02.22
4Q 2022 annual review: no significant changes; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	06.23.22	11.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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