Clinical Policy: Trientine (Cuvrior, Syprine)

Reference Number: ERX.SPA.255
Effective Date: 12.01.18
Last Review Date: 08.22
Line of Business: Commercial, Medicaid

Revision Log

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

Description

Trientine tetrahydrochloride (Cuvrior™) and trientine hydrochloride (Syprine®) are chelating agents.

FDA Approved Indication(s)

Cuvrior is indicated for the treatment of adult patients with stable Wilson's disease who are de-coppered and tolerant to penicillamine.

Syprine is indicated for the treatment of patients with Wilson's disease who are intolerant of penicillamine.

Limitation(s) of use: Unlike penicillamine, Syprine is not recommended in cystinuria or rheumatoid arthritis. Syprine is not indicated for treatment of biliary cirrhosis.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Cuvrior and Syprine are **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. One of the following (a or b):
   a. Cuvrior: Age ≥ 18 years;
   b. Syprine: Age ≥ 6 years;
3. Failure of generic penicillamine (*generic of Cuprimine® is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed one of the following (a or b):
   a. Cuvrior: 3,000 mg (10 tablets) per day;
   b. Syprine (i or ii):
      i. Age > 12 years: 2,000 mg per day;
      ii. Age ≤ 12 years: 1,500 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;

2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Cuvrior: 3,000 mg (10 tablets) per day;
   b. Syprine (i or ii):
      i. Age > 12 years: 2,000 mg per day;
      ii. Age ≤ 12 years: 1,500 mg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents;
B. Biliary cirrhosis;
C. Cystinuria;
D. Rheumatoid arthritis.

IV. Appendices/General Information

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

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
penicillamine (Depen®, Cuprimine®)	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)

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.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): hypersensitivity
- Boxed warning(s): none reported

Appendix D: General Information
- Clinical experience with Syprine is limited, and alternate dosing regimens have not been well-characterized; all endpoints in determining an individual patient's dose have not been well defined.
- Syprine and penicillamine cannot be considered interchangeable.
- The absence of a sulfhydryl moiety renders Syprine incapable of binding cystine and, therefore, it is of no use in cystinuria. In 15 patients with rheumatoid arthritis, Syprine was reported not to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment.
- The differences in the FDA-approved indications for Cuvrior and Syprine are due to differing clinical trial design. The clinical trial supporting the Syprine FDA application was conducted in patients with Wilson's disease intolerant of penicillamine, while the clinical trial for Cuvrior was performed in stable de-coppered Wilson's disease patients who were tolerant to penicillamine. In the latter trial, Cuvrior was compared to and found to be non-inferior to penicillamine.

- There are currently no clinical data that investigate any differences in either efficacy or safety of different trientine salts in patients either tolerant or intolerant to penicillamine. Once the trientine salt is broken down in the gut, the active moiety of trientine is the same for both salts.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Cuvrior*	300 mg up to 3,000 mg PO BID. Refer to the prescribing information for detail on switching from pencillamine or other trientine products to Cuvrior	3,000 mg/day
Syprine	Age ≤ 12 years: 500-750 mg/day PO in divided doses two, three, or four times daily Age > 12 years: 750-1,250 mg/day PO in divided doses two, three, or four times daily	≤ 12 years: 1,500 mg/day > 12 years: 2,000 mg/day

**Cuvrior is not substitutable on a milligram-per-milligram basis with other trientine products*

VI. Product Availability

Drug Name	Product Availability
Cuvrior	Tablet: 300 mg
Syprine	Capsule: 250 mg

VII. References

1. Cuvrior Prescribing Information. Chicago, IL: Orphalan; April 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215760s000lbl.pdf. Accessed May 6, 2022.
2. Syprine Prescribing Information. Bridewater, NJ: Bausch Health Companies Inc.: September 2020. Available at: www.syprine.com. Accessed May 6, 2022.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology-ip.com/.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	08.07.18	11.18
4Q 2019 annual review: no significant changes; references reviewed and updated.	08.26.19	11.19
4Q 2020 annual review: no significant changes; references reviewed and updated.	08.03.20	11.20
4Q 2021 annual review: no significant changes; references reviewed and updated.	08.02.21	11.21
RT4: added new dose form, Cuvrior; updated Appendix D with information regarding the difference in FDA indications for Cuvrior and Syprine.	05.06.22	08.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.