penicillamine (Cuprimine®)/trientine (Syprine®, Cuvrior™), generics

Policy # 00531
Original Effective Date: 01/01/2017
Current Effective Date: 08/12/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider penicillamine capsules (Cuprimine®)‡ and trientine-based products (Syprine®, Cuvrior™)‡, both brand and generic, to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for penicillamine capsules (Cuprimine) or trientine-based products (Syprine, Cuvrior), both brand and generic, will be considered when the following criteria are met for the requested drug:

- If the requested drug is brand or generic penicillamine capsules (Cuprimine): There is clinical evidence or patient history that suggests the use of generic penicillamine tablets (generic of Depen) will be/was ineffective or will/did cause an adverse reaction to the patient; OR
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- If the requested drug is branded trientine hydrochloride (Syprine): Patient has a diagnosis of Wilson's disease; AND
  - Patient is intolerant of a penicillamine product; AND

  - Patient has tried and failed (e.g., intolerance, inadequate response) generic trientine hydrochloride unless there is clinical evidence or patient history that suggests the use of generic trientine hydrochloride will be ineffective or cause an adverse reaction to the patient; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- If the requested drug is branded trientine tetrahydrochloride (Cuvrior): Patient has a diagnosis of Wilson's disease; AND
  - Patient is 18 years of age or older; AND
  - Patient has been de-coppered (for example, a non-ceruloplasmin copper [NCC] level ≤150 mcg/L); AND
  - Patient has previously tolerated one penicillamine product; OR
- If the requested drug is generic trientine hydrochloride: Patient has a diagnosis of Wilson's disease AND the patient is intolerant of a penicillamine product.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brand or generic penicillamine capsules (Cuprimine) WITHOUT clinical evidence or patient history that suggests the use of generic penicillamine tablets (generic of Depen) will be/was ineffective or will/did cause an adverse reaction to the patient to be **not medically necessary.****

Based on review of available data, the Company considers the use of branded trientine hydrochloride (Syprine) when the patient has NOT tried and failed (e.g., intolerance, inadequate response) generic trientine hydrochloride to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of trientine-based products (Syprine, Cuvrior), both brand and generic, for any indication other than their respective U.S. Food and Drug Administration (FDA) approved indications to be **investigational.***

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Background/Overview

Cuprimine and Depen, which both contain 200 mg of penicillamine, are both indicated for the treatment of Wilson's disease, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. The main difference between the two is that Depen is a tablet while Cuprimine is a capsule. Both products are available in generic form. There is also a vast difference in price, making Depen, and subsequently its generic, the more economical options with equal clinical efficacy as Cuprimine and its generic. At the time of this publication, the generic of Depen, penicillamine tablet, is the most economical option for therapy. Syprine, or trientine hydrochloride, is indicated for the treatment of Wilson's disease in those that are intolerant to penicillamine. Syprine is a drug that has a very specific FDA approval and should be managed as such. Syprine has a generic equivalent available. It is available as 250 mg capsules.

Cuvrior is a copper chelator that has a similar active ingredient, trientine, though differing in salt form, as Syprine, but a slightly different indication. Cuvrior is indicated for the treatment of adult patients with stable Wilson's disease who are de-coppered and tolerant to penicillamine. It is available as a 300 mg tablet. A generic is not yet available for Cuvrior.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Cuprimine and Depen, which both contain 200 mg of penicillamine, are both indicated for the treatment of Wilson's disease, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. Syprine is indicated for the treatment of Wilson's disease in those that are intolerant to penicillamine. Cuvrior is indicated for the treatment of patients with stable Wilson's disease who are de-coppered and tolerant to penicillamine.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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The patient selection criteria presented in this policy take into consideration clinical evidence or patient history that suggests the use of generic penicillamine tablets (generic of Depen) will be/was ineffective or will/did cause an adverse reaction to the patient. Based on a review of the available data and in the absence of the above mentioned caveat, there is no advantage of using brand or generic Cuprimine over generic penicillamine tablets (generic of Depen). This policy is meant to ensure that Syprine and Cuvrior are being used for their labeled indications as well as to ensure that the generic trientine products are being used prior to their respective brand (for example, generic trientine hydrochloride being used before brand Syprine).

References

1. Syprine [package insert]. Valeant Pharmaceuticals International. Bridgewater, New Jersey. Updated June 2014.
2. Cuprimine [package insert]. Valeant Pharmaceuticals International. Bridgewater, New Jersey. Updated November 2015.
3. Depen [package insert]. Meda Pharmaceuticals. Somerset, New Jersey. Revised April 2009.
4. Cuvrior [package insert]. Orphalon SA. Chicago, Illinois. Updated April 2022.

Policy History

Original Effective Date: 01/01/2017
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09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. New policy.
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. A generic to Syprine is now available and will be required prior to use of the branded Syprine. Added "generics" to the title.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Added the Cuprimine generic to the policy.

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05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Added another generic trientine product, Clovique, to the policy.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. A generic to Depen tablets is now available, so the requirement to use Depen has been updated to use generic penicillamine tablets.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Changed title from "penicillamine (Cuprimine®)/trientine (Syprine®), generics" to "penicillamine (Cuprimine®)/trientine (Syprine®, Cuvrior™), generics." Removed mentioning of Clovique because it is discontinued. Added new product, Cuvrior, to policy with criteria.
07/02/2024	Medical Policy Committee review
07/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.