# Clinical Policy: Copper Histidinate (Zycubo)

Reference Number: CP.PHAR.714
Effective Date: 01.12.26
Last Review Date: 05.26
Line of Business: Commercial, HIM/ICHRA, Medicaid

Coding Implications
Revision Log

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

## Description

Copper histidinate (Zycubo®) is a copper supplement.

## FDA Approved Indication(s)

Zycubo is indicated for the treatment of Menkes disease in pediatric patients.

Limitation(s) of use: Zycubo is not indicated for the treatment of occipital horn syndrome.

## 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 Zycubo is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Menkes Disease** (must meet all)**:**

1. Diagnosis of Menkes disease confirmed by one of the following methods (a or b):
   a. Genetic testing demonstrating mutation in the ATP7A gene;
   b. Both of the following (i and ii):
      i. Biochemically with one of the following (1, 2, or 3):
         1) Low serum copper levels (< 75 mcg/dL);
         2) Low ceruloplasmin;
         3) Abnormal plasma catecholamine levels (*see Appendix D*);
      ii. Clinically based on signs of abnormal hair color/texture, seizures, hypotonia, or developmental delay;
2. Member does not have occipital horn syndrome (*see Appendix D*);
3. Age < 17 years;
4. Prescribed by or in consultation with a neonatologist, neurologist, or specialist with expertise in the management of metabolic disorders (e.g., pediatric geneticist);
5. Documentation of baseline (within the last 30 days) serum copper and ceruloplasmin levels;
6. Dose does not exceed one of the following (a or b):
   a. Age < 1 year: 2.9 mg per day;
   b. Age ≥ 1 year: 1.45 mg per day.

**Approval duration: 6 months**

**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/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; 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, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. Menkes Disease** (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 as evidenced by, including but not limited to, improvement in any of the following parameters:
   a. Serum copper level increase;
   b. Serum ceruloplasmin level increase;
   c. Improvement in neurologic symptoms (e.g., reduction in seizure frequency, improvement in muscle tone and motor skills);
3. Age < 17 years;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Age < 1 year: 2.9 mg per day;
   b. Age ≥ 1 year: 1.45 mg per day.

**Approval duration:**
**Medicaid/HIM/ICHRA –** 12 months
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**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/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; 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, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

## 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, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents;
**B.** Occipital horn syndrome (s*ee Appendix D*).

## IV. Appendices/General Information

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

*Appendix B: Therapeutic Alternatives*
Not applicable

*Appendix C: Contraindications/Boxed Warnings*
None reported

*Appendix D: General Information*

- Menkes disease can be detected by relatively high concentrations of dopamine and its metabolites compared to norepinephrine and its metabolites, presumably because dopamine-beta-hydroxylase requires copper as a co-factor. The following ratios can be used in the diagnosis of Menkes disease:
  - Plasma dopamine/norepinephrine ratio with values > 0.2
  - Plasma dihydroxyphenylacetic acid/dihydroxyphenylglycol ratio with values > 5
- Occipital horn syndrome is a distinct, typically milder ATP7A-related phenotype characterized by residual copper transport activity and predominantly connective-tissue manifestations rather than the early, severe neurodegeneration and high early mortality that defined the overall-survival endpoint used in the pivotal trial for Zybuco's approval. Due to this residual copper transport activity in those with occipital horn syndrome, administering a high-potency copper histidinate product such as Zybuco may lead to over-supplementation and risk of copper overload with associated complications such as nephrotoxicity and hepatoxicity.

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| Menkes disease | • Age < 1 year: 1.45 mg (250 mcg elemental copper) SC BID<br>• Age ≥ 1 year to < 17 years: 1.45 mg (250 mcg elemental copper) SC QD | See dosing regimen |

## VI. Product Availability

Single-dose vial, lyophilized powder: 2.9 mg of copper histidinate, equivalent to 0.5 mg of elemental copper

## VII. References

1. Zycubo Prescribing Information. Sentynl Therapeutics, Inc.; Solana Beach, CA: January 2026. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/211241s000lbl.pdf.. Accessed January 29, 2026.
2. ClinicalTrials.gov. Molecular bases of response to copper treatment in Menkes disease, related phenotypes, and unexplained copper deficiency. Available at: https://clinicaltrials.gov/study/NCT00811785. Accessed January 21, 2026.
3. ClinicalTrials.gov. Copper histidinate treatment for Menkes disease. Available at: https://clinicaltrials.gov/study/NCT04074512. Accessed January 21, 2026.
4. ClinicalTrials.gov. Copper histidine therapy for Menkes diseases. Available at: https://clinicaltrials.gov/study/NCT00001262. Accessed February 3, 2026.
5. Cyprium Therapeutics: Corporate Presentation. December 2021. Available at: https://www.cypriumtx.com/wp-content/uploads/2021/12/Cyprium_Corporate_Presentation_December-2021.v01.pdf. Accessed January 21, 2026.
6. Kaler SG, Munim S, Chen M, et al. Poster: Copper histidinate treatment for Menkes disease (Kinky hair syndrome). Presented at the American Academy of Pediatrics National Conference & Exhibition, October 8–12, 2021. Available at: https://www.cypriumtx.com/wp-content/uploads/2021/10/Kaler-et-al-AAP-Poster_final-draft_24SEP2021.pdf. Accessed January 21, 2026.
7. Vairo FPE, Chwal BC, Perini S, et al. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. Mol Genet Metab. 2019 Jan;126(1):6-13.
8. Kaler SG. Neurodevelopment and brain growth in classic Menkes disease is influenced by age and symptomatology at initiation of copper treatment. J Trace Elem Med Biol. 2014 Oct;28(4):427-30. doi: 10.1016/j.jtemb.2014.08.008.

## Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|---|---|
| J3590 | Unclassified biologics |
| C9399 | Unclassified drugs or biologicals |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created pre-emptively | 02.11.25 | 05.25 |
| Drug is now FDA-approved – criteria updated per FDA labeling; added upper age limit of 17 years; added requirement for documentation of baseline (within the last 30 days) serum copper and ceruloplasmin levels; added requirement that member does not have occipital horn syndrome; for continued therapy positive response, added serum levels or neurologic symptom parameters. Added ICHRA line of business. | 03.26.26 | 05.26 |

**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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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