Clinical Policy: Copper Histidinate (Zycubo)

Reference Number: PA.CP.PHAR.714
Effective Date: 05/2026
Last Review Date: 04/2026

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 PA Health & Wellness® 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

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
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: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53

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 • 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
Policy created	04/2026