VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Menkes Disease – Zycubo Prior Authorization Policy
- Zycubo™ (copper histidinate subcutaneous injection – Sentynl)

REVIEW DATE: 02/04/2026; selected revision 02/11/2026, 03/11/2026, 03/18/2026

OVERVIEW

Zycubo, a copper replacement product, is indicated for the treatment of Menkes disease in pediatric patients.[1] The prescribing information specifies dosing for patients < 17 years of age.

Limitations of Use: Zycubo is not indicated for the treatment of Occipital Horn Syndrome (OHS). OHS is a milder phenotype of Menkes disease.[1]

Disease Overview

Menkes disease is a rare, X-linked, neurodegenerative disease caused by a defect in the ATP7A gene.[2,3] This gene encodes an enzyme that is responsible for copper absorption and transport throughout the body. Copper is an essential trace element that plays a crucial role in several metabolic processes. Mutations in the gene result in poor distribution of copper, resulting in low serum concentrations of copper and ceruloplasmin, a copper bound protein. Menkes disease is characterized by seizures, failure to gain weight and grow, developmental delays, and intellectual disability. Other manifestations include abnormalities of the vascular system, bladder, bowel, bones, muscles, and nervous system. The three most well known phenotypes of Menkes disease are classical disease, intermediate Menkes disease, and OHS; of these, classical disease is the most severe. Children with classical disease (90% of cases) develop symptoms in infancy and typically do not live past three years of age.[3,4] As such, a systematic review and expert consensus panel recommend early initiation of subcutaneous copper histidine therapy during the neonatal period (before 30 days of life) in infants with a confirmed diagnosis of classical disease.[4] Treatment should be continued indefinitely. A presumed diagnosis may be confirmed by plasma catecholamine analysis or molecular genetic analysis.[3,4] Plasma dopamine/norepinephrine ratios (values > 0.2) or dihydroxyphenylacetic acid/dihydroxyphenylglycol ratios (values > 5) are recognized as diagnostic for Menkes disease. However, plasma catecholamine analysis is not available at all centers. In these scenarios, genetic confirmation of pathogenic/likely pathogenic variants in the ATP7A gene is recommended.[4,5] Although serum copper and ceruloplasmin (copper-bound protein) are low in Menkes disease, levels are typically low in infants less than six months of age. Therefore, biochemical labs are not used independently for diagnostic confirmation.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zycubo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zycubo as well as the monitoring required for adverse events and long-term efficacy, approval requires Zycubo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zycubo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Menkes Disease.** Approve for the duration noted if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is < 17 years of age; AND
   - **B)** The diagnosis is established by ONE of the following (i, ii, or iii):
     - **i.** Approve for 1 year if the patient has a molecular genetic test demonstrating a pathogenic or likely pathogenic variant in the *ATP7A* gene; OR
     - **ii.** Approve for 1 year if the patient has plasma catecholamine analysis findings that are consistent with the diagnosis; OR
       Note: Plasma dopamine/norepinephrine ratios (values > 0.2) or dihydroxyphenylacetic acid/dihydroxyphenylglycol ratios (values > 5) are diagnostic for Menkes disease.
     - **iii.** Approve for 1 month if according to the prescriber, the patient has findings suggestive of Menkes disease and genetic testing or plasma catecholamine analysis is in progress; AND
   - **C)** The medication is prescribed by or in consultation with a geneticist, neonatologist, neurologist, or a specialist who focuses on the treatment of Menkes disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zycubo is not recommended in the following situations:

1. **Occipital Horn Syndrome**. Zycubo is not indicated for the treatment of Occipital Horn Syndrome, a milder phenotype of Menkes disease.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zycubo™ subcutaneous injection [prescribing information]. Solana Beach, CA: Sentynl; January 2026.
2. Menkes Disease. National organization for rare disorders NORD. Updated March 24, 2020. Available at: https://rarediseases.org/rare-diseases/menkes-disease/. Accessed on January 13, 2026.
3. Ramani PK, Parayil Sankaran B. Menkes Disease. [Updated 2023 Nov 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560917/. Accessed on January 13, 2026.
4. Vairo FPE, Chwal BC, et al. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. *Mol Genet Metab*. 2019;126(1):6-13.
5. Kaler SG, DiStasio AT. ATP7A-Related Copper Transport Disorders. 2003 May 9 [Updated 2021 Apr 15]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1413/. Accessed on January 13, 2026.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/04/2026
Selected Revision	**Menkes Disease**: The specialist requirement was updated to include a neonatologist.	02/11/2026
Selected Revision	**Menkes Disease**: A requirement that the patient is < 18 years of age was added.	03/11/2026
Selected Revision	**Menkes Disease**: The age requirement was modified to < 17 years of age.	03/18/2026