Drug Coverage Policy

Effective Date.....08/01/2026
Coverage Policy Number.....IP0794
Policy Title.....Zycubo

Menkes Disease – Zycubo

- Zycubo™ (copper histidinate subcutaneous injection – Sentynl)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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.

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POLICY STATEMENT
Prior Authorization is required for 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.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information. For a patient case in which the documentation requirement of a molecular genetic test or plasma catecholamine analysis findings that are consistent with the diagnosis of Menkes Disease has been previously provided, the documentation requirement in this *Menkes Disease – Zycubo Prior Authorization Policy* is considered to be met.

Zycubo is considered medically necessary when the following is met:

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 **[documentation required]**; OR

ii. Approve for 1 year if the patient has plasma catecholamine analysis findings that are consistent with the diagnosis **[documentation required]**; 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 Covered

Zycubo for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs

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.

Revision Details

Summary of Changes	Review Date	Effective Date
New policy	03/26/2026	05/15/2026
Updated the policy title from "Zycubo for Individual and Family Plans" to "Menkes Disease – Zycubo."	05/14/2026	08/01/2026

The policy effective date is in force until updated or retired.

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