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

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.

CIGNA NATIONAL FORMULARY COVERAGE:

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.

- **Zycubo™ (copper histidinate subcutaneous injection – Sentynl)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

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 COVERED

- **Zycubo™ (copper histidinate subcutaneous injection – Sentynl) is(are) considered not medically necessary for ANY other use(s) 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]

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