

copper histidinate (Zycubo[®])[‡]

Policy # 00982

Original Effective Date: 08/01/2026

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider copper histidinate (Zycubo[®])[‡] for the treatment of Menkes disease to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for copper histidinate (Zycubo) for the treatment of Menkes disease will be considered when the patient selection criteria are met:

Initial Authorization (6 months):

- Patient has a diagnosis of Menkes disease; AND
- Documentation is provided that the diagnosis has been confirmed by ONE of the following:
 - Genetic testing demonstrating a severe pathogenic variant in *ATP7A* associated with Menkes disease (e.g., duplication/deletion, nonsense, or a canonical splice junction variant); OR
 - Plasma catecholamine levels consistent with Menkes disease, including ONE of the following:
 - Plasma dopamine to norepinephrine ratio greater than 0.2; OR
 - Dihydroxyphenylacetic acid (DOPAC) to dihydroxyphenylglycol (DHPG) ratio greater than 5; AND
- Patient is 17 years of age or younger; AND
- Patient does not have occipital horn syndrome; AND
- Patient does not have Wilson disease; AND
- Patient does not have pre-existing liver disease (e.g., hepatitis, biliary atresia, cirrhosis); AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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- Patient does not have renal impairment (defined as serum creatinine greater than 1.0 mg/dL); AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Baseline laboratory evaluation is completed prior to initiation of therapy with Zycubo and includes all of the following: serum copper and ceruloplasmin levels; serum electrolytes; kidney function (i.e., BUN, creatinine); liver function (i.e., AST, ALT, bilirubin); and complete blood count (CBC); AND
- Laboratory monitoring is performed during treatment with Zycubo in accordance with FDA labeling (i.e., every 6 weeks for the first 6 months, then every 3 months for 18 months, then every 6 months thereafter).

Continuation:

- Patient has received an initial authorization for Zycubo; AND
- Patient is 17 years of age or younger; AND
- Patient is experiencing a clinically meaningful response to therapy, as evidenced by documentation of clinical benefit or disease stabilization, which may include improvement or maintenance of neurologic function, growth parameters, or copper levels; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Laboratory monitoring will continue to be performed during treatment with Zycubo in accordance with FDA labeling.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers copper histidinate (Zycubo) when the patient has pre-existing liver disease or renal impairment with a serum creatinine greater than 1.0 mg/dL to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of copper histidinate (Zycubo) when the patient has not experienced a clinically meaningful response to therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of copper histidinate (Zycubo) when the patient selection criteria are not met (except those noted above as **not medically necessary****) to be **investigational.***

Background/Overview

Zycubo is a copper replacement product indicated for the treatment of Menkes disease (MD) in pediatric patients. It is the first treatment approved by the Food and Drug Administration (FDA) for MD and was granted Orphan Drug, Rare Pediatric Disease, Breakthrough Therapy, and Fast Track designations by the FDA. Zycubo is not approved for the treatment of occipital horn syndrome (OHS). Menkes disease, also known as Menkes kinky hair syndrome, is a rare, X-linked recessive disorder of copper metabolism, with an estimated incidence of approximately 1 in 100,000 live births. It is caused by pathogenic variants in the *ATP7A* gene, which encodes a protein responsible for the absorption and distribution of copper throughout the body. Deficiency or dysfunction of this protein results in impaired intestinal absorption of copper, reduced transport of copper to the brain, and decreased activity of multiple copper-dependent enzymes, leading to low serum concentrations of copper and ceruloplasmin. The severity of the phenotype varies based on the degree of residual *ATP7A* function, with the three most well-known phenotypes being classical Menkes disease, mild Menkes disease, and occipital horn syndrome. Classical Menkes disease is the most severe form and is associated with near-complete loss of *ATP7A* function. It typically presents in early infancy, often around 2 to 3 months of age, after an initial period in which affected infants may appear healthy. Clinical features may include loss of early developmental milestones, hypotonia, seizures, failure to thrive, characteristic sparse or kinky hair, and distinctive facial features. Without early copper replacement therapy, classical Menkes disease progresses to severe neurodegeneration and death, typically in early childhood. OHS is a clinically distinct and generally milder form of *ATP7A*-related disease. It is associated with partial *ATP7A* function and primarily causes connective tissue manifestations, dysautonomia, and subtle neurocognitive deficits. Because patients with OHS retain some copper transport activity, use of a high-potency copper histidinate product such as Zycubo could lead to excess copper levels and increase the risk of toxicity, including nephrotoxicity and hepatotoxicity. Diagnosis is primarily confirmed through identification of pathogenic or likely pathogenic variants in the *ATP7A* gene. Biochemical testing may provide supportive evidence; however, traditional markers such as serum copper and ceruloplasmin are not reliable in young infants, as levels are physiologically low during the neonatal period and should not be used alone to establish the diagnosis. Plasma catecholamine analysis can aid in diagnosis by demonstrating abnormalities consistent with impaired copper-dependent enzyme activity, including elevated dopamine to norepinephrine ratios (values > 0.2) or increased dihydroxyphenylacetic acid to dihydroxyphenylglycol ratios (values > 5). These specialized tests are not universally available; therefore, molecular genetic testing remains the preferred method for confirmation. Early diagnosis is critical, as timely initiation of copper replacement therapy is associated with improved clinical outcomes. This is particularly important given that copper deficiency leads to early-onset, progressive neurologic decline, developmental delay, epilepsy, poor growth, and multisystem involvement. Clinical manifestations generally appear in early infancy and include developmental delay, seizures, hypopigmented and brittle (“kinky”) hair, growth failure, and skeletal abnormalities. Disease severity and life expectancy may vary. Prior management has included off-label use of parenteral copper replacement (e.g., copper histidinate) initiated as soon as possible after birth, which has been associated with improved survival when started within the first weeks of life. Treatment response, however, is variable and influenced by the ability of copper to cross the gastrointestinal tract and blood-brain barrier, as well as the extent of residual copper transport related to the underlying *ATP7A* mutation. Supportive care may also include management of seizures, nutritional support, physical and occupational therapy, and treatment of autonomic instability.

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Zycubo is supplied as a 2.9 mg lyophilized powder in a single-dose vial for reconstitution and is stored under refrigeration. The recommended dosage varies by age. Pediatric patients younger than 1 year receive 1.45 mg twice daily (8 to 12 hours between injections), and patients 1 year of age to less than 18 years of age receive 1.45 mg once daily. Administration is by subcutaneous injection and may be performed by a caregiver if appropriately trained. Baseline laboratory evaluation prior to treatment includes serum copper and ceruloplasmin levels, serum electrolytes, renal and hepatic function, and complete blood count. Ongoing monitoring is required during therapy, with laboratory assessments every 6 weeks for the first 6 months, then every 3 months for the next 18 months, and every 6 months thereafter. Dose adjustments or treatment interruption may be considered in the setting of laboratory abnormalities as described within the package insert.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Zycubo is indicated for the treatment of Menkes disease in pediatric patients. Zycubo is not indicated for the treatment of Occipital Horn Syndrome.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Zycubo was evaluated in pediatric patients with Menkes disease (age at treatment initiation ranges from 0.1 to 31.4 months) receiving 3 years of copper histidinate treatment in two open-label, single-arm clinical trials (Trial 1 and Trial 2). Data from Zycubo-treated patients in these two trials were compared to data from an untreated contemporaneous external control cohort as collected under a protocol amendment of Trial 2. In both trials, pediatric patients less than 1 year of age received 1.45 mg of Zycubo administered subcutaneously twice daily until 1 year of age, and pediatric patients equal to or greater than 1 year of age received 1.45 mg of Zycubo subcutaneously once daily for up to 3 years. Overall survival was evaluated in a subset of the pooled population from Trial 1 and Trial 2, referred to as the pooled efficacy population. This efficacy population included only patients with Menkes disease who carried a severe pathogenic variant of the *ATP7A* gene (duplication/deletion, nonsense, or a canonical splice junction variant) and were born after 1999. There were 83 pediatric patients (66 Zycubo; 17 external control) in this pooled efficacy population: 21 patients (21 Zycubo) from Trial 1 and 62 patients (45 Zycubo; 17 external control) from Trial 2. Patients in the pooled efficacy population were assigned to 1 of 4 cohorts:

- Zycubo-Early Treatment (Zycubo-ET): Zycubo started within 4 weeks of birth.
- Zycubo-Late Treatment (Zycubo-LT): Zycubo started after 4 weeks of birth.
- External Control-Early Treatment (EC-ET): No prior Zycubo or copper treatment, asymptomatic for significant neurological signs and symptoms approximately 4 weeks after birth, and survived 4 weeks after diagnosis.
- External Control-Late Treatment (EC-LT): Subset of EC-ET cohort, diagnosed with MD after 4 weeks of birth, and survived ≥ 2 weeks after diagnosis.

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The primary efficacy analysis compared the overall survival in patients in the Zycubo-ET and EC-ET cohorts. Patients in the Zycubo-ET cohort (patients treated with Zycubo) had a significant improvement in overall survival compared to patients in the EC-ET cohort, with a 78% reduction in the risk of death. In the Zycubo-ET cohort, 15 (48%) patients survived > 6 years, including 7 (23%) patients who survived > 12 years. In the EC-ET cohort, no patients survived > 6 years. The secondary efficacy analysis compared the overall survival in patients in the Zycubo-LT cohort with patients in the EC-LT cohort. Patients in the Zycubo-LT cohort (patients treated with Zycubo) had a significant improvement in overall survival compared to patients in the EC-LT cohort, with a 73% reduction in the risk of death. In the Zycubo-LT cohort, 11 (31.4%) patients survived > 6 years, including 1 patient (2.9%) who survived > 12 years. In the EC-LT cohort, no patients survived > 6 years.

References

1. Zycubo subcutaneous injection [prescribing information]. Solana Beach, CA: Sentyln; January 2026.
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3. 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.
4. Kaler SG, Holmes CS, et al. Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med*. 2008;358(6):605-14.
5. Zycubo Drug Evaluation. Express Scripts. January 2026.
6. Zycubo New Drug Review. IPD Analytics. February 2026.
7. Vairo FP, Chwal BC, et al. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. *Molecular Genetics and Metabolism*. 2019;126(1): 6–13.

Policy History

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07/21/2026 Pre Pharmacy and Therapeutics Committee review

07/22/2026 Pharmacy and Therapeutics Committee approval. New Policy.

Next Scheduled Review Date: 07/2027

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

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diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.