Original Effective Date: 06/11/2026
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Last P&T Approval/Version: 04/29/2026
Next Review Due By: 04/2027
Policy Number: C30655-A

Zycubo (copper histidinate)

PRODUCTS AFFECTED

Zycubo (copper histidinate)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Menkes Disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. This clinical policy will be reviewed along with state and federal requirements, the benefit being administered and formulary preferencing. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available. The Pharmacy and Therapeutics Committee has determined that biosimilars may be preferred.

A. MENKES DISEASE:
   1. Documentation of a presumptive diagnosis or a diagnosis of Menkes disease as evidenced by one of the following [DOCUMENTATION REQUIRED]:

a) Genetic testing confirming ATP7A gene mutation AND biochemical evidence consistent with severe Menkes disease phenotype (e.g., dopamine-β-hydroxylase deficiency and abnormal dopamine-to-norepinephrine ratios)
OR
b) Documentation of clinical signs and symptoms consistent with a diagnosis of Menkes disease: characteristic hair abnormalities (e.g., sparse, hypopigmented, brittle, and crinkly hair), osteoporosis, seizures, hypotonia, unstable body temperature, failure to thrive (or slow physical development), developmental delay or regression

AND

2. Documentation of baseline serum copper and ceruloplasmin levels to be used to evaluate efficacy of therapy at renewal

CONTINUATION OF THERAPY:

A. MENKES DISEASE:

1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
2. Documentation of a positive clinical response, as demonstrated by improvement of serum copper and ceruloplasmin levels compared with baseline
AND
3. Documentation of improvement in the signs and symptoms of the condition including normalization of hair abnormalities, improved bone health, decreased seizure frequency, increased muscle tone, stabilization of body temperature, improved growth parameters, or achievement of developmental milestones.
AND
4. Genetic test confirming ATP7A gene mutation and biochemical evidence (e.g., dopamine-β-hydroxylase deficiency and abnormal dopamine-to-norepinephrine ratios) confirming diagnosis of Menkes disease if initial authorization was based on presumptive diagnosis [DOCUMENTATION REQUIRED]
NOTE: Zycubo should be discontinued if Menkes disease is not confirmed by genetic test and biochemical evidence.

DURATION OF APPROVAL:

Initial authorization: 3 months (presumptive diagnosis), 12 months (diagnosis confirmed with genetic test and biochemical evidence)
Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified neonatologist, neurologist, metabolic specialist, or geneticist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Up to 16 years of age

QUANTITY:

Less than 1 year of age: 1.45 mg twice daily
1 year to 16 years of age: 1.45 mg once daily

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Trace Minerals

FDA-APPROVED USES:
Indicated for the treatment of Menkes disease in pediatric patients.
Limitations of Use: Zycubo (copper histidinate) is not indicated for the treatment of Occipital Horn Syndrome.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Menkes disease (MD) is a rare, inherited X-linked neurodegenerative disorder caused by pathogenic mutations in the ATP7A gene, resulting in defective copper transport and systemic copper deficiency. Affected infants typically appear normal at birth but develop hypotonia, seizures, failure to thrive, and progressive neurodevelopmental decline within the first months of life, with high mortality in early childhood. Characteristic findings include connective tissue abnormalities and distinctive hypopigmented, kinky hair. Disease severity spans a spectrum from classic, severe MD to milder phenotypes such as occipital horn syndrome.

Loss of ATP7A function disrupts delivery of copper to the central nervous system and other tissues, impairing multiple copper-dependent enzymes critical for neurologic function, energy metabolism, antioxidant defense, and connective tissue integrity. Early diagnosis is essential, as treatment initiated in the neonatal period, particularly in patients with residual ATP7A function, can improve survival and neurodevelopmental outcomes. However, no standardized treatment guidelines existed historically, and care was largely supportive, with off-label use of compounded injectable copper histidinate producing variable results.

Zycubo (copper histidinate) is the first FDA-approved therapy for the treatment of Menkes disease in pediatric patients. Zycubo restores and maintains copper levels, addressing the underlying pathophysiology of MD. It represents a significant advance over compounded copper products by providing a standardized, regulated treatment option intended for early initiation to optimize neurologic outcomes. Zycubo is not indicated for occipital horn syndrome.

The efficacy of Zycubo (copper histidinate) was evaluated in pediatric patients with Menkes disease in two open-label, single-arm clinical trials, with treatment durations of up to 3 years. Treatment was initiated between 0.1 and 31.4 months of age. Outcomes in patients treated with Zycubo were compared with an untreated, contemporaneous external control (EC) cohort collected under a protocol amendment to Trial 2.

The primary efficacy endpoint was overall survival (OS). The pooled efficacy population included 83 pediatric patients with severe pathogenic ATP7A variants (duplication/deletion, nonsense, or canonical splice-site mutations) born after 1999, comprising 66 patients in the Zycubo group and 17 untreated EC patients. Patients were stratified by timing of treatment initiation into early treatment (ET; ≤4 weeks of life, corrected for prematurity) and late treatment (LT; >4 weeks).

In the primary efficacy analysis, early treatment with Zycubo resulted in a statistically significant and clinically meaningful improvement in OS compared with untreated EC patients, with a 78% reduction in the risk of death (hazard ratio [HR], 0.22; 95% CI, 0.10–0.49). Median survival was 177.1 months in the Zycubo-ET cohort versus 17.6 months in the EC-ET cohort. In the secondary analysis, patients treated later also

demonstrated a significant survival benefit, with a 73% reduction in the risk of death compared with EC-LT patients (HR, 0.27; 95% CI, 0.12–0.57) and improved median survival (62.4 vs 20.7 months).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Zycubo (copper histidinate) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Zycubo (copper histidinate) include: no labeled contraindications.

Exclusions/Discontinuation:
Copper Accumulation and Risk of Toxicity: Treatment with Zycubo (copper histidinate) may lead to further copper accumulation and has the potential to result in drug-induced kidney injury, liver dysfunction, and hematological abnormalities.

After initiating Zycubo, monitor laboratory values every 6 weeks for the first 6 months, then every 3 months for 18 months, and then every 6 months thereafter during Zycubo treatment. If laboratory abnormalities are detected, consider reducing the frequency of Zycubo administration or temporarily withholding or permanently discontinuing Zycubo.

OTHER SPECIAL CONSIDERATIONS:
A caregiver may administer Zycubo (copper histidinate) to patients after proper training in subcutaneous injection technique if a healthcare provider determines that it is appropriate.

Zycubo must be reconstituted with 0.9% sodium chloride prior to administration. Administer reconstituted Zycubo solution using a sterile disposable 1 mL syringe and 1/2 inch injection needle (between 23 to 27 gauge). Inject 0.5 mL of reconstituted Zycubo solution subcutaneously at separate sites in the abdominal area (2 inches from the navel), buttocks, and the outer lateral aspect of the upper arm or thigh. Rotate injection sites with each injection to reduce the risk of lipodystrophy. Do not give injections into areas where the skin is scarred, tender, bruised, red, or hard.

Discard unused portion after each single use. Do not administer more than one dose from the vial.

For pediatric patients younger than 1 year, administer Zycubo dose (1.45 mg twice daily) as two vials daily, with injections spaced 8 to 12 hours apart.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Zycubo SOLR 2.9MG single-dose vial for reconstitution

REFERENCES

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8. National Institutes of Health. (n.d.). Copper histidinate in patients with Menkes disease (ClinicalTrials.gov Identifier: NCT00811785). ClinicalTrials.gov. Retrieved March 24, 2026, from https://clinicaltrials.gov/study/NCT00811785

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q2 2026