Drug Use Research & Management Program
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Orphan Drug Evaluation: Zycubo (copper histidinate) powder for injection

Date of Review: June 2026
Generic Name: Copper histidinate

End Date of Literature Search: 3/31/26
Brand Name (Manufacturer): Zycubo (Sentynl Therapeutics)

Dossier Received: No

Purpose for Review:

- To review evidence of safety and effectiveness of copper histidinate injection for pediatric patients with Menkes disease.
- To establish prior authorization (PA) criteria to support medical appropriateness and necessity.
- The estimated wholesale acquisition cost (WAC) per member over 12 months is $681,455 to $1,362,910 based on $1867/2.9mg syringe copper histidinate (equivalent to 0.5 mg elemental copper). Dosing is 1.45 mg copper histidinate once or twice daily subcutaneously based on age. A reconstituted vial is stable when refrigerated at (36°F to 46°F) for up to 24 hours. Package insert instructs to discard unused portion after each use; do not administer more than one dose from the vial.[1]

Plain Language Summary:

- Menkes disease is a rare, inherited condition that occurs when the body cannot absorb enough copper or move copper properly to different places in the body. It affects mostly boys and is usually diagnosed in the first year of life.
- People with Menkes disease can have many symptoms, including seizures, delayed development. It usually causes death by three years of age. Occipital Horn Syndrome is a less severe version of this disease that does not usually cause symptoms until ages 5 to 10 years, and people with it may live past 50 years of age.
- In 2026, the Food and Drug Administration (FDA) approved copper histidinate injection (ZYCUBO) to treat children and adolescents with Menkes disease. It is not approved for Occipital Horn Syndrome.[1]
- In 66 people with Menkes disease who were treated with copper histidinate, survival over a 3-year period was better than when compared to historic records of patients who did not receive copper histidinate treatment. This was true for people who started treatment both before (early treatment) and after 4 weeks of age (late treatment).
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for copper histidinate injection in patients with Menkes disease who are receiving appropriate monitoring and dosing. The provider must document medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the effectiveness and safety of copper histidinate injection for pediatric patients with Menkes disease?
2. Are there subpopulations based on age, symptom severity, or other demographics for which copper histidinate injection is more effective or safe?

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Conclusions:

- There is low-quality data of improved survival from two pooled, open-label studies of copper histidinate treatment compared to historic controls in patients with Menkes disease. Survival in the early treatment group (N=31) where copper histidinate was started within 4 weeks of birth was 52% versus 12% in the historic control group (N=17) with a hazard ratio (HR) of 0.22 (95% confidence interval [CI] 0.10 to 0.49) at the end of treatment (up to 36 months). Survival in the late treatment group (N=35) where copper histidinate treatment was started later than 4 weeks after birth was 34% versus 12% in the historic control (N=16) with a HR of 0.27 (95% CI 0.12 to 0.57).[1,2]
- There is insufficient evidence for safety.[1] All data is from open-label, uncontrolled research. There is a theoretical concern for copper toxicity due to accumulation in certain organ systems over time, specifically kidneys, liver, and hematopoietic system and monitoring for toxicity is recommended in the package labeling.[1]
- There is insufficient evidence for use of copper histidinate in treating symptoms of Occipital Horn Syndrome.[1]

Recommendations:

- Implement PA criteria to verify appropriate diagnosis, monitoring and dosing.

Background:

- Menkes disease (MD) is an X-linked disorder associated with severe copper deficiency due to inadequate intestinal uptake.[2] MD is caused by *ATP7A* mutations, affecting transmembrane copper-transporting P-type ATPase in enterocytes and across the blood-brain barrier.[2,3] Extracellular efflux of copper is also affected by *ATP7A*, and accumulation is seen in all tissues except liver and brain.[2] There is some genotype-phenotype correlation for certain mutations, but it is difficult to predict phenotype perfectly from mutation type.[2,4]
- The disease is a progressive condition with primarily neurologic symptoms such as developmental delay and epilepsy. Bony abnormalities may also occur. Classical Menke (90% of cases) is usually fatal between age 6 months and 3 years.[2] Intermediate-phenotype Menke disease is generally milder with 5-10% prevalence within MD diagnosis. Patients can present similarly to classic disease or live to adulthood. Occipital Horn Syndrome (OHS), with prevalence of approximately 3% of MD cases and has the least severe presentation. Symptoms appear at age 5 to 10 years for patients with OHS. Patients with OHS have slightly low to normal levels of copper and ceruloplasmin, often have bony exostoses described as occipital horns on skull radiographs, and may live to be over 50 years old.[2]
- Copper histidinate is considered standard of care for MD, though no FDA approved product was available historically.[2]
- Incidence is estimated at 1:50,000 to 1:250,000 live male births.[2]
- Serum copper and ceruloplasmin concentrations are low in patients with MD. Ceruloplasmin is the most common copper-binding protein transporter. Healthy newborns may often have low copper and ceruloplasmin levels, making these assessments alone inadequate for diagnosis of MD.[2]
- Testing is not on the Oregon newborn screening panel.[5]
- In the Oregon Health Plan, there are 14 patients with the E83.09 diagnosis (other disorders of copper metabolism), which includes other diagnoses in addition to Menkes disease. Most of these identified patients are female and over age 18 years, making it unlikely that most of these patients have Menkes disease based on the demographics.

Drug Information

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy and Safety:

Clinical trials used to support FDA approval are described and evaluated below in **Table 1**. Noteworthy trial design and patient characteristics include:

- Trial duration: Treatment administered up to age of 1 year using twice daily dosing; after 1 year of age, dosing was decreased to once daily, for up to 3 years. Treatment duration ranged between 1.1 and 36 months.[1]
- Number of participants: 129 in the safety analysis (median exposure duration 24 months [range 1 to 39 months]) and 66 patients who met final inclusion criteria for MD who were treated and analyzed for efficacy.[1]
- Comparator: External control (historic) cohort collected under a protocol amendment.[2] Early treatment historic controls had no prior ZYCUBO or copper treatment, were asymptomatic for significant neurological signs and symptoms at approximately 4 weeks after birth, and survived at least 4 weeks after diagnosis.[1] Late treatment historic controls were a subset of the historic control-early treatment groups who were diagnosed with MD after 4 weeks since birth and survived at least 2 weeks after diagnosis.[2]
- Key inclusion criteria: Menkes disease with severe pathogenic variant of *ATP7A* gene (duplication/deletion, nonsense, or a canonical splice junction variant); born after 1999.[1] Inclusion criteria for both studies were changed via protocol amendments and originally included additional conditions (e.g. occipital horn syndrome, unexplained copper deficiency) as diagnosis criteria used only clinical features and biochemical profiles (study 0149) and low copper concentration (study 0059) resulting in larger safety population than the final efficacy population.[2] Patients in the historic control group were born during or after 2000, overlapping with the drug treatment population.[2]
- Key exclusion criteria: diagnosis of Wilson disease, any disease that may adversely affect gastrointestinal absorption, history of cerebrovascular accident, and chronic/severe cardiac disease.[1]
- Baseline disease severity and population characteristics: Most patients were male (98%), White (63%) and had premature birth (66-77% in treatment groups; 81-82% in historic controls).[1] The most common *ATP7A* mutation variant was nonsense (51.2%- 71%).[2]
- Setting: Majority of patients from United States (94.3-100% copper histidinate cohorts; 62.5-64.7% historic cohorts). Most remaining patients were from Europe.[2]
- Magnitude of benefit and clinical relevance of results: Both the early treatment (within 4 weeks of birth) and late treatment (after 4 weeks from birth) showed significant benefits compared to historic controls for overall survival and estimated median survival. The early treatment group (52%) and late treatment group (34%) survival was significantly improved over the historic controls (12% for both historic cohorts) at the end of the evaluation period.[1] Estimated median survival time was longer for both the early treatment group (177.1 months, 95% CI 33 to not estimable) compared to historic control (17.6 months, 95% CI 11.5 to 28.6), and for the late treatment group (62.4 months, 95% CI 29.6 to 80.7) compared to the historic control (20.7, 95% CI 12.6 to 28.6). [1]
- Safety signals: Due to the pathophysiology of MD with impaired copper transport throughout the body, patients with MD may have copper accumulation and organ impairment, particularly in the kidneys, liver, and hematopoietic system. It is anticipated the supplemental copper could increase accumulation and toxicity.[1] Risk may be higher for those under 2 years of age due to the immaturity of the hepatic and renal systems at that age.[1] Dose adjustment is not recommended based only on serum copper or ceruloplasmin, however, should be considered if other lab work indicate potential toxicity.[1] The FDA has recommended a post-marketing study to characterize the serum copper and ceruloplasmin concentrations in patients with MD.[2] Full adverse reaction table from package insert is summarized in **Table 2**.

- Subgroup analyses: FDA ran nine sensitivity analyses due to data discrepancies with censored dates (e.g., date of last contact), dates of death, gene variant status and documentation of gene variant status.[2] These analyses were performed to address issues with quality of the efficacy and safety data, clinical heterogeneity and lack of genotype-phenotype correlation, and comparability of the external control to the treated cohorts.[2] All of the sensitivity analyses demonstrated consistent survival benefit. [2]

See **Table 1** for major evidence limitations including:

- Full risk of bias assessment unable to be performed due to unpublished study and protocol. There is risk of selection bias of single arm study with protocol amendment to add historic control cohort. Lack of documentation of past medical history of external control subjects' onset of symptoms was noted, though survival data was considered verifiable. There was significant attrition overall and a large percentage for undescribed "other" reasons.

Table 1. Comparative Evidence Table.[1,2]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Trial 1 (0149) Phase 1/2 NCT00001262 Trial 2 (0059) Phase 3 NCT00811785 OL, SA, N=129 safety N=83	1. CuHis 1.45 mg SC Once daily if age 1 year and older Twice daily if under 1 year old Duration up to 3 years	<u>Demographics</u>: -Age-range 0 to 48 months -Male 98% -White 63% -Hispanic 13% -Black 10% -Premature birth 66-77% treatment groups, 81-82% control cohorts -Most common *ATP7A* variant nonsense (56.2-71.0%) <u>Key Inclusion Criteria</u>: -Menkes disease with -severe pathogenic variant of *ATP7A* (duplication/deletion, nonsense, or a canonical splice junction variant) -Born after 1999 <u>Key Exclusion Criteria</u>: -Pre-existing liver or kidney disease -History of bleeding diatheses	<u>Cohorts</u> CuHis-ET N=31 HC-ET N=17 CuHis-LT N=35 HC-LT N=16 Attrition: CuHis-ET 12/31 (38.7%) CuHis-LT 24/35 (68.6%)	<u>Primary Endpoint</u>: Survival of CuHis-ET versus HC-ET Patients alive # (%): CuHis-ET 16 (52%) HC-ET 2 (12%) Estimated Median survival time using Kaplan-Meier method (mo): CuHis-ET 177.1 (95% CI, 33 to NE) HC-ET 17.6 (95% CI, 11.5 to 28.6) HR 0.22 (95% CI, 0.1 to 0.49) <u>Secondary Endpoint</u>: Survival of CuHis-LT versus HC-LT Patients alive # (%): CuHis-LT 12 (34%) HC-LT 2 (12%) Estimated Median survival time using Kaplan-Meier method (mo): CuHis-LT 62.4 (95% CI, 29.6 to 80.7) HC-LT 20.7 (95% CI, 12.6 to 29.6) HR 0.27 (95% CI, 0.12 to 0.57) CuHis-LT 11 (34%) of patients survived > 6 years, 1 patient (2.9%) survived > 12 years. HC-LT no patient survived > 6 years	0.4/ 3 0.22/ 5	<u>D/C due to AE:</u> Cu-His ET 7 (22.6%) Cu-His LT 11 (31.4%) Cardiac (10.1% pooled) and respiratory, thoracic, & mediastinal (7% pooled) disorders most common cause for d/c	NA	**Studies are unpublished and full risk of bias assessment unable to be performed.** **Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (High) Single arm study. Original study inclusion criteria narrowed for analysis as clinical features and low copper concentration are not adequate for MD diagnosis. Historic control cohort added via protocol amendment during second trial. <u>Performance Bias</u>: (Unclear) Methods not fully published, though primary outcome is objective. Potential differences in other care associated with study participation versus historic control. <u>Detection Bias</u>: (Unclear) Final efficacy outcome objective after protocol changes from other outcomes. Safety monitoring strategy unclear. <u>Attrition Bias</u>: (Unclear) Missing data noted in FDA summary. If death dates were unknown, patients were censored at the last known date alive. High rates of overall study discontinuation, with 12.9% (CuHis-ET) and 20.0% (CuHis-LT) due to "other" causes (not AE, withdrawal of consent, or LTFU). <u>Reporting Bias</u>: (Unclear) Study and protocol unpublished. Multiple protocol amendments as medical knowledge of the disease changed over time. <u>Other Bias:</u> (Unclear) Original sponsorship/research through NIH. First transferred to Cyprium Therapeutics, Inc. and later to Sentynl Therapeutics. **Applicability**:

		-Wilson disease -Disease affecting gastrointestinal absorption -Chronic/severe cardiac disease						Patient: Most patients are male, which is representative of disease population. Some racial diversity noted in study population. Intervention: Dose chosen based on 1989 case series of 4 patients, not clinical PK or dose ranging studies. Comparator: Historic controls with concerns for missing data. Outcomes: Survival is appropriate for progressive, fatal condition. Assessment of quality of life and neurological development/milestones would be useful. Setting: Almost all treatment patients were from the US; most historic controls were from the US or Europe.
Abbreviations: AE = adverse event; CI = confidence interval; CuHis = copper histidinate; D/C = discontinue; ET = early treatment; FDA = Food and Drug Administration; HC-ET = historic control early treatment; HC-LT = historic control-late treatment; HR = hazard ratio; LT = late treatment; LTFU = lost to follow up; MD = Menke disease mo = months; N = number of subjects; NA = not applicable; NE = not estimable; NIH = National Institutes of Health; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PK = pharmacokinetic; PP = per protocol; SA = single arm; SC = subcutaneously; US = United States.								

Table 2: Adverse Events occurring in at least 7% of Patients with Menkes Disease[1]

Adverse Events	Menkes Disease N=129 N (%)
Pneumonia	38 (30)
Viral Infection	35 (27)
Respiratory failure • Cardiopulmonary failure	30 (23) • 11 (9)
Seizure	29 (23)
Bacterial infection • Renal and urinary tract infection	26 (20) • 12 (9)
Hemorrhage	23 (18)
Hypotension	20 (16)
Vomiting	19 (15)
Tachycardia	16 (12)
Pyrexia	16 (12)
Volume depletion	16 (12)
Fracture	16 (12)
Dyspnea	16 (12)
Transaminases elevation	13 (10)
Diarrhea	13 (10)
Fungal infection	12 (9)
Anemia	11 (9)
Local administration reaction	9 (7)

References:

1. Zycubo (copper histidinate). package insert. Solana Beach, Ca. Sentynl Therapeutics Inc. Jan 2026.
2. Food and Drug Administration. Integrated Review NDA 211241. Completed 1/5/26. Accessed 3/10/26. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2026/211241Orig1s000IntegratedR.pdf.
3. Vairo FPE, Chwal BC, Perini S, Ferreira MAP, de Freitas Lopes AC, Saute JAM. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. *Mol Genet Metab*. Jan 2019;126(1):6-13. doi:10.1016/j.ymgme.2018.12.005
4. De Feyter S, Beyens A, Callewaert B. ATP7A-related copper transport disorders: A systematic review and definition of the clinical subtypes. *Journal of Inherited Metabolic Disease*. 03 2023;46(2):163-173. doi:https://dx.doi.org/10.1002/jimd.12590
5. NW Regional Newborn Bloodspot Screening Program. Newborn Bloodspot Screening Practitioner's Manual, 16th Edition; 2026 Available at: https://www.oregon.gov/oha/PH/LABORATORYSERVICES/NEWBORNSCREENING/Documents/Practitioner%20Manual.pdf.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYCUBO safely and effectively. See full prescribing information for ZYCUBO.

ZYCUBO® (copper histidinate) for injection, for subcutaneous use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
ZYCUBO is a copper replacement product indicated for the treatment of Menkes disease in pediatric patients. (1)

Limitations of Use
ZYCUBO is not indicated for the treatment of Occipital Horn Syndrome. (1)

----------DOSAGE AND ADMINISTRATION----------
- Before initiating ZYCUBO, obtain baseline serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count. (2.1)
- The recommended dosage of ZYCUBO in pediatric patients:
  - Less than 1 year of age is 1.45 mg twice daily (8-12 hours between injections). (2.2)
  - 1 year of age to less than 17 years of age is 1.45 mg once daily. (2.2)
- Monitor serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC). (2.3)
- Reconstitute ZYCUBO and administer subcutaneously. (2.4, 2.6)
- See Full Prescribing Information for additional preparation, storage, and administration instructions. (2.4, 2.5, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection: 2.9 mg of copper histidinate (equivalent to 0.5 mg elemental copper) as a lyophilized powder or cake in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
Copper Accumulation and Risk of Toxicity: Treatment with ZYCUBO may lead to further copper accumulation and has the potential to result in drug-induced kidney injury, liver dysfunction, and hematological abnormalities. Monitor patients during ZYCUBO treatment. Adjust dosage if necessary. (2.2, 5.1, 6.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥7%) were pneumonia, viral infection, respiratory failure, seizure, bacterial infection, hemorrhage, hypotension, vomiting, tachycardia, pyrexia, volume depletion, fracture, dyspnea, transaminases elevation, diarrhea, fungal infection, anemia, and local administration reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sentynl Therapeutics, Inc. at 1-888-507-5206 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2026

Appendix 2: Proposed Prior Authorization Criteria

Copper histidinate (ZYCUBO)

Goal(s):
- Promote appropriate use of copper histidinate based on available evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- Copper histidinate (ZYCUBO)

Covered Populations: FFS and CCO patients beginning 05/1/26 (pharmacy or provider administered claims)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a patient with a prior FFS approval for the requested drug?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved age and indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is patient both treatment naïve AND over 3 years of age?	**Yes**: Go to #5	**No:** Go to #6
5. Is there documentation that Occipital Horn Disease has been ruled out?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the drug prescribed by or in consultation with a specialist with experience treating Menkes disease (e.g., medical geneticist, pediatric neurologist)?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documentation of baseline lab work within past 3 months including: serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC)?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested dose/interval appropriate based on FDA labeling?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there documentation of genetic testing indicating severe loss of function variant of *ATP7A* gene (mutation types: deletion/duplication, nonsense, or canonical splice junction variants)?	**Yes**: Pass to RPh; Pend. Refer to DMAP for secondary review. Approve based on age: < 12 months: enough units to reach 1st birthday with twice daily dosing; ≥ 12 months: approve for 6 months enough units for once daily dosing. Note: all vials are single use only.	**No:** Go to #10

Approval Criteria		
10. Is genetic testing pending?	**Yes**: Pass to RPh; Pend. Refer to DMAP for secondary review. Approve for one month while awaiting results. Dose based on age: < 12 months: twice daily dosing; ≥ 12 months: once daily dosing Note: all vials are single use only.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of appropriate laboratory monitoring based on labeling recommendations and current length of therapy? Note: product labeling recommends serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and CBC every 6 weeks for first 6 months, then every 3 months for 18 months, and then every 6 months thereafter while on treatment.	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is dosing interval appropriate based on FDA labeling and *current* age? Note: dosing should be adjusted to once daily after 1 year of age.	**Yes:** Pass to RPh; Pend. Refer to DMAP for secondary review. Approval duration: 12 months	**No:** Pass to RPh. Deny; medical appropriateness