Sentynl Therapeutics Inc. Announces FDA Approval of ZYCUBO® (*copper histidinate*)

ZYCUBO® is now the first and only therapy approved for the treatment of Menkes disease in the United States

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Sentynl Therapeutics Inc. ("**Sentynl**"), a U.S.-based biopharmaceutical company wholly-owned by Zydus Lifesciences Limited ("**Zydus Group**"), announced that the U.S. Food and Drug Administration ("**FDA**") has approved ZYCUBO® (copper histidinate) for the treatment of Menkes disease in pediatric patients. This is the first and only treatment approved for Menkes disease, a rare and fatal genetic condition, in the United States. ZYCUBO® is not indicated for the treatment of Occipital Horn Syndrome.

"Approval is a pivotal step towards achieving our goal of making a meaningful impact on patients, caregivers, and the rare disease community," said Dr. Sharvil P. Patel, Managing Director, Zydus Lifesciences Limited. "This milestone marks a transformative moment for the Zydus Group and for families affected by Menkes disease. For the first time, patients have access to an approved therapy, offering hope where no options existed. We are proud to advance patient care and deliver innovative solutions to those who need them most."

Menkes disease is a rare X-linked recessive pediatric disease caused by mutations of the copper transporter ATP7A encoded by the *ATP7A* gene. Patients with Menkes disease are born with the inability to absorb dietary copper and subsequently have impaired copper transport across the blood-brain barrier, and, until now, there has been no approved treatment in the United States. ZYCUBO® is a subcutaneous injectable formulation of copper histidinate that restores copper homeostasis and maintains copper levels in patients with Menkes disease. (Estimated birth prevalence of Menkes disease and ATP7A-related disorders based on the Genome Aggregation Database (gnomAD) and Menkes disease | European Journal of Human Genetics)

"Menkes disease presents significant challenges for patients and their families. With no known cure, most untreated patients do not survive beyond three years of age," said Matt Heck, CEO, Sentynl. "FDA's approval serves as compelling affirmation that a safe and effective therapy is now available for patients living with this devastating disease."

The approval is supported by positive topline clinical efficacy results for ZYCUBO, demonstrating statistically significant improvement in overall survival for Menkes disease subjects who received early treatment ("**ET**") with ZYCUBO, compared to an untreated contemporaneous external control cohort, with a nearly 80% reduction in the risk of death. Median overall survival ("**OS**") was 177.1 months for ZYCUBO ET cohort compared to 17.6 months for the untreated contemporaneous external control cohort. (U.S. Prescribing Information)

The 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.

“This milestone represents the culmination of decades of research into better understanding and ultimately finding an effective treatment for Menkes disease,” said Dr. Stephen Kaler, a clinical genetics and genomics specialist at the Columbia University Medical Center. “Increased awareness of Menkes disease and rapid testing upon suspicion are critical, as beginning copper histidinate therapy in affected neonates has been shown to reduce symptoms and prolong life.”

Acquired from Cyprium Therapeutics in 2023, Sentynl has advanced ZYCUBO through the final stages of development with the FDA based on positive results from pivotal studies, receiving Breakthrough Therapy, Fast Track, Rare Pediatric Disease, and the FDA Orphan Drug Designations. Copper histidinate has also been granted Orphan Designation by the European Medicines Agency.

About Menkes Disease

Menkes disease is a rare X-linked recessive pediatric disease caused by gene mutations of the copper transporter ATP7A. The minimum birth prevalence for Menkes disease is believed to be 1 in 34,810 live male births, and potentially as high as 1 in 8,664 live male births, based on recent genome-based ascertainment. (Estimated birth prevalence of Menkes disease and ATP7A-related disorders based on the Genome Aggregation Database (gnomAD)). The condition is characterized by distinctive clinical features, including sparse and depigmented hair (“kinky hair”), connective tissue problems, and severe neurological symptoms such as seizures, hypotonia, failure to thrive, and neurodevelopmental delays. Mortality is high in untreated Menkes disease, with many patients dying between 2-3 years of age. (Early clinical signs and treatment of Menkes disease - ScienceDirect). Milder versions of *ATP7A* mutations are associated with conditions other than Menkes Disease, such as Occipital Horn Syndrome and *ATP7A*-related Distal Motor Neuropathy.

About ZYCUBO® (copper histidinate)

ZYCUBO® is the first and only FDA-approved, bioavailable copper replacement therapy for the treatment of Menkes disease, a copper transport deficiency caused by mutations in *ATP7A*. ZYCUBO is a subcutaneous injectable formulation of copper histidinate that is given daily to deliver elemental copper to the body. In a pooled analysis of two open label, single-arm clinical trials, early treatment with ZYCUBO (ZYCUBO-ET) demonstrated significant improvement in overall survival for Menkes disease patients with a nearly 80% reduction in the risk of death compared to the overall survival of patients in the untreated contemporaneous external control cohort. (Copper Histidinate Treatment for Menkes Disease (Kinky Hair Syndrome) | Pediatrics | American Academy of Pediatrics) For more information, visit https://zycubo.com.

INDICATIONS AND USAGE

ZYCUBO is indicated for the treatment of Menkes disease in pediatric patients.

Limitations of Use

ZYCUBO is not indicated for the treatment of Occipital Horn Syndrome.

IMPORTANT SAFETY INFORMATION

Contraindications
None.

Warnings and Precautions

Copper Accumulation and Risk of Toxicity

Impaired copper transport in patients with Menkes disease can lead to copper accumulation and organ impairment in the kidneys, liver, and hematopoietic system. Treatment with ZYCUBO may lead to further copper accumulation and related toxicity, especially in the first two years of life given renal and hepatic immaturity.

Renal Dysfunction

Kidney injury has been reported in patients taking ZYCUBO. In patients with Menkes disease, kidney dysfunction may already be present from the accumulation of copper in the kidneys. This may be worsened from the administration of copper in ZYCUBO. The healthcare team will monitor your child's kidney function through periodic laboratory tests before and during ZYCUBO administration. The dose of ZYCUBO may be adjusted as appropriate based on the results of the laboratory tests.

Liver Dysfunction

Copper accumulation can result in liver dysfunction. The healthcare team will monitor your child's liver function through periodic laboratory tests before and during ZYCUBO administration. The dose of ZYCUBO may be adjusted as appropriate based on the results of the laboratory tests.

Hematological Abnormalities

Copper accumulation with ZYCUBO can result in spleen and bone marrow dysfunction as well as interference with iron metabolism. Anemia has been reported in patients taking ZYCUBO for Menkes disease. The healthcare team will perform periodic laboratory tests (complete blood count) before and during ZYCUBO administration. The dose of ZYCUBO may be adjusted as appropriate based on the results of the laboratory tests.

Adverse Reactions

The most common adverse reactions (≥7%) were pneumonia (30%), viral infection (27%), respiratory failure[1] (23%) (including cardiopulmonary failure (9%)), seizure (23%), bacterial infection[2] (20%) (including renal and urinary tract infection (9%)), hemorrhage (18%), hypotension (16%), vomiting (15%), tachycardia (12%), pyrexia (12%), volume depletion (12%), fracture (12%), dyspnea (12%), transaminases elevation (10%), diarrhea (10%), fungal infection (9%), anemia (9%), and local administration reaction (7%).

Use in Specific Populations

Pregnancy

Risk Summary

There are no available data on ZYCUBO use during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with ZYCUBO.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Lactation

Risk Summary

There are no available data on the presence of ZYCUBO in either human or animal breast milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYCUBO and any potential adverse effects on the breastfed infant from ZYCUBO or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of ZYCUBO for the treatment of Menkes disease have been established in pediatric patients. Use of ZYCUBO for this indication is supported by evidence from two clinical trials. Data from patients in these two trials were compared to data from an untreated contemporaneous external control cohort.

Geriatric Use

Menkes disease is a disease of pediatric patients. Clinical trials of ZYCUBO did not include patients 65 years of age and older.

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full U.S. Prescribing Information including Instructions for Use (IFU) for ZYCUBO®.

[1] Respiratory failure consists of multiple similar terms including cardiopulmonary failure.

[2] Bacterial infection consists of multiple similar terms including renal and urinary tract infection.

About Zydus Lifesciences Limited

Zydus Lifesciences Limited is an innovation-led life-sciences company with leadership positions across pharmaceuticals and consumer wellness, supported by an emerging MedTech franchise and a global footprint across the United States, India and other international markets. As of September 30, 2025, the group employs 29,000 people worldwide including 1,500 scientists engaged in R&D, and is driven by its mission to unlock new possibilities in life sciences through quality healthcare solutions that impact lives. The group aspires to transform lives through path-breaking discoveries. For more details visit www.zyduslife.com

About Sentynl Therapeutics Inc

Sentynl Therapeutics Inc. ("**Sentynl**") is a commercial stage U.S.-based biopharmaceutical company focused on bringing innovative therapies to patients living with rare diseases. Recognized for its commitment to the rare disease community, Sentynl leverages its global operations as well as its parent organization, Zydus Group, to advance the development, manufacturing, and delivery of treatments to patients who need them in numerous countries worldwide. Sentynl is dedicated to improving patient outcomes and access while upholding ethical standards and operating in compliance with applicable laws, regulations, and industry guidelines. For more information, visit https://sentynl.com.

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