ZYCUBO- copper histidinate injection, powder, lyophilized, for solution
Sentynl Therapeutics, Inc.

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: Exogenous administration of copper 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.

Revised: 1/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing Before Initiating ZYCUBO

Before initiating ZYCUBO, obtain baseline serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC) *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage and Administration

The recommended dosage of ZYCUBO in pediatric patients:

- Less than 1 year of age is 1.45 mg administered subcutaneously twice daily (8-12 hours between injections).
- 1 year of age to less than 17 years of age is 1.45 mg administered subcutaneously once daily.

2.3 Dosage and Administration Modifications and Monitoring

Monitor serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC) 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. Return to increased frequency of laboratory evaluation when resuming a dosage as clinically indicated *[see Warnings and Precautions (5.1)]*.

2.4 Preparation Instructions

Preparation

- Use aseptic technique during preparation. Reconstitute ZYCUBO using a sterile disposable 3 mL syringe and 1 inch needle (between 16 to 22 gauge) (*see Instructions for Use*).
- Remove 1 ZYCUBO vial from the refrigerator and set aside for approximately 30 minutes to allow the vial to come to room temperature [20°C to 25°C (68°F to 77°F)] before use.
- Reconstitute ZYCUBO by tilting the vial and slowly injecting 1 mL of 0.9% Sodium Chloride Injection, USP down the inside wall of the vial.
- Gently swirl the vial continuously until the powder is completely dissolved. Do not shake the vial. Each vial will yield a concentration of 2.9 mg/mL.
- Visually inspect the reconstituted solution in the vial for particulate matter and discoloration. The solution should be blue. Discard if particles are present or the solution is discolored (not blue) or cloudy.
- Do not mix with other medications.

2.5 Storage of Reconstituted Solution

If the reconstituted ZYCUBO vial is not used immediately, store the vial refrigerated at 2°C to 8°C (36° to 46°F) for up to 24 hours or at controlled room temperature at 20°C to 25°C (68°F to 77°F) for up to 4 hours.

Discard the reconstituted ZYCUBO vial if not used within 24 hours of refrigeration or within 4 hours at room temperature.

2.6 Administration Instructions

A caregiver may administer ZYCUBO to patients after proper training in subcutaneous injection technique if a healthcare provider determines that it is appropriate (*see Instructions for Use*). Administer ZYCUBO using a sterile disposable 1 mL syringe and 1/2 inch injection needle (between 23 to 27 gauge).

Slowly withdraw 0.5 mL of reconstituted ZYCUBO solution from the vial and inject

subcutaneously.

Administer ZYCUBO by subcutaneous injection 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.

2.7 Missed Dose

If a ZYCUBO dose is missed, administer the missed dose as soon as possible. Administer the next scheduled dose at least 6 hours after the administration of the missed dose.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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.

Obtain baseline serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC). 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. Return to increased frequency of laboratory monitoring when resuming a dosage as clinically indicated.

Drug-Induced Kidney Injury

Copper accumulation with ZYCUBO use has the potential to result in renal tubular toxicity in patients with Menkes disease. Routinely monitor patients starting or re-starting ZYCUBO for signs and symptoms of renal tubular toxicity. New-onset or worsening non-anion gap metabolic acidosis may be a sign of drug-related renal tubular acidosis. Increased urinary beta-2 microglobulin and/or new-onset hypophosphatemia, hyponatremia, or hypokalemia may be signs of drug-related proximal renal tubular toxicity. Provide supportive care with electrolyte repletion and supplementation as clinically indicated.

Copper accumulation with ZYCUBO use has the potential to result in glomerular injury, leading to decreased kidney function or new-onset proteinuria.

Liver Dysfunction

Copper accumulation with ZYCUBO can result in liver dysfunction. Elevations of liver transaminases have been reported in patients taking ZYCUBO for Menkes disease *[see Adverse Reactions (6.1)]*. Single cell necrosis, inflammation, and fibrosis, along with increased liver transaminases and bilirubin were observed in studies conducted over 13-weeks in juvenile rats with normal baseline copper levels *[see Use in Specific Populations (8.4)].*

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 *[see Adverse Reactions (6.1)]*. Increased cellularity and pigmented macrophages in the spleen and increased hematological values were observed in studies conducted over 13-weeks in normal juvenile rats *[see Use in Specific Populations (8.4)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Copper Accumulation and Risk of Toxicity: Drug-Induced Kidney Injury, Liver Dysfunction, Hematological Abnormalities *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety analysis from 2 open-label, single-arm clinical trials included a total of 129 ZYCUBO-treated patients with an age range from 0 to 48 months. Patients less than 1 year of age received ZYCUBO 1.45 mg twice daily, and patients 1 year of age and older received ZYCUBO 1.45 mg once daily. The median exposure duration was 24 months (range: 1 to 39 months) *[see Clinical Studies (14)]*.

Serious Adverse Reactions

Serious adverse reactions reported in ≥5% of ZYCUBO-treated pediatric patients with Menkes disease were pneumonia, dehydration, seizure, respiratory distress, respiratory syncytial virus infection, cardiopulmonary failure, upper respiratory tract infection, respiratory failure, and vomiting.

Common Adverse Reactions

Table 1 lists the most common adverse reactions that occurred in ≥7% of patients in the pooled safety analysis during an observation period ranging from 1 to 39 months.

Table 1. Adverse Reactions Occurring in ≥7% Patients with Menkes Disease

(Trial 1 and Trial 2)

Adverse Reactions	**Menkes Disease (N = 129)** **N (%)**
Pneumonia	38 (30)
Viral infection	35 (27)
Respiratory failure[1]	30 (23)
Cardiopulmonary failure	11 (9)
Seizure	29 (23)
Bacterial infection	26 (20)
Renal and urinary tract infection[2]	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)

[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.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.2 Lactation

Risk Summary

There are no data on the presence of copper histidinate and its metabolites in either human or animal 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.

8.4 Pediatric Use

The safety and effectiveness of ZYCUBO for the treatment of Menkes disease have been established in pediatric patients, and the information on this use is discussed throughout the labeling.

Juvenile Animal Toxicity Data

Juvenile rats with normal baseline copper levels were administered copper histidinate from postnatal day (PND) 10 (the equivalent of a human newborn) to PND 100 (the equivalent of a human adult) subcutaneously twice daily for 13 weeks at 1, 2, and 5 mg/kg. Histopathological findings were observed in the kidney (tubular necrosis, eosinophilic globules), liver (single cell necrosis, inflammation, fibrosis), and spleen (increased cellularity and pigmented macrophages), in addition to increased liver transaminases (ALT, AST) and bilirubin, and decreased red blood cells, hemoglobin and hematocrit at 5 mg/kg (10-fold the human plasma concentration at the recommended dose of ZYCUBO (based on C_{max})). Changes in liver (necrosis, inflammation, ALT, AST) and kidney (eosinophilic globules) were also noted as low as 1 mg/kg (equivalent to human plasma concentration at the recommended dose of ZYCUBO (based on C_{max})). A no-observed-adverse-effect-level (NOAEL) in juvenile rats could not be determined. Proportional increases in copper and ceruloplasmin levels occurred with increasing dose levels.

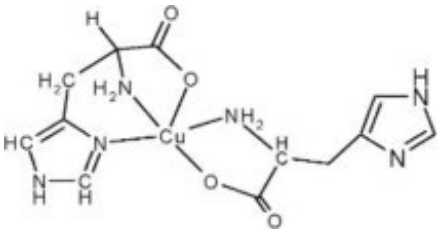
8.5 Geriatric Use

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

11 DESCRIPTION

ZYCUBO (copper histidinate) for injection is a copper replacement product. The chemical name is copper, (L-histidinato-$\varkappa N$,$\varkappa N3$,$\varkappa O$)(L-histidinato-$\varkappa N$,$\varkappa O$)-, (*SP*-5-14-C)-. The molecular formula is $C_{12}H_{16}CuN_6O_4$, and the molecular weight is 371.84 g/mol. Copper histidinate is soluble in water.

The chemical structure is:



ZYCUBO is a sterile, preservative-free, blue lyophilized powder or cake for subcutaneous injection after reconstitution with 1 mL sterile 0.9% Sodium Chloride Injection, USP. Each single-dose vial contains 2.9 mg of copper histidinate (equivalent to 0.5 mg elemental copper). The resultant solution has a concentration of 2.9 mg/mL and a pH of 7.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Menkes disease is an X-linked recessive disorder caused by pathogenic variants in the copper transport ATPase encoded by *ATP7A*. Patients with Menkes disease have impaired absorption of copper from their diet, impaired transport of copper across the blood-brain barrier, and dysregulation of many copper-dependent enzymes. ZYCUBO is a bioavailable copper replacement therapy that is administered as a subcutaneous injection to bypass the impaired gastrointestinal absorption observed in patients with Menkes disease.

12.2 Pharmacodynamics

Patients with Menkes disease have low serum concentrations of copper and ceruloplasmin. Treatment with ZYCUBO increases serum copper and ceruloplasmin concentrations in patients with Menkes disease.

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of ZYCUBO have not been fully characterized.

12.3 Pharmacokinetics

The geometric mean (CV%) maximum serum concentration (C_{max}) of copper histidinate was 67 (36%) ng/mL, the geometric mean (CV%) area under the concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24hr}$) was 186 (21%) ng•hr/mL, and the geometric mean (CV%) area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) was 296 (15%) ng•hr/mL following a single subcutaneous dose of 3 mg copper histidinate (approximately twice the approved recommended dose for Menkes disease patients 1 year old or older) in healthy adult subjects.

At the recommended dosage, the mean (SD) serum copper concentration increased from a baseline concentration of 30 (25) mcg/dL to 114 (38) mcg/dL at 12 months, and gradually decreased over the 36-month treatment period, with a mean (SD) serum copper concentration of 63 (31) mcg/dL at 36 months. The mean (SD) serum ceruloplasmin concentration was 12 (12) mg/dL at baseline, 33 (11) mg/dL at 12 months, and 20 (8) mg/dL at 36 months *[see Clinical Studies (14)]*.

Absorption

The absolute bioavailability of copper histidinate following subcutaneous injection has not been determined. The median time to reach maximum serum concentrations of copper histidinate (T_{max}) was 0.75 hours following a single subcutaneous dose of 3 mg copper histidinate (approximately twice the approved recommended dose for Menkes disease patients 1 year old or older) in healthy adult subjects.

Distribution

The mean (SD) apparent volume of distribution (Vz/F) of copper histidinate during the terminal elimination phase was 1034 (588) L following a single subcutaneous dose of 3 mg copper histidinate (approximately twice the approved recommended dose for Menkes disease patients 1 year old or older) in healthy adult subjects.

Serum copper histidinate concentration-time profiles exhibited an initial decrease followed by a terminal elimination phase, consistent with the release of copper from the

copper histidinate complex to the carrier proteins ceruloplasmin and albumin, followed by incorporation of copper histidinate and histidine into the endogenous pools of copper histidinate and histidine, respectively.

No binding of copper histidinate to human plasma proteins *in vitro* has been observed.

Elimination

The mean (SD) serum clearance (CL/F) of copper histidinate was 10.3 (1.6) L/hr, and the mean terminal half-life was 75 hours following a single subcutaneous dose of 3 mg copper histidinate (approximately twice the approved recommended dose for Menkes disease patients 1 year old or older) in healthy adult subjects.

Metabolism

The metabolism of copper histidinate has not been well characterized.

Excretion

Elimination of elemental copper is through biliary excretion.

Drug Interaction Studies

In vitro Studies: Copper histidinate is a weak inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6 (IC_{50} >100 µM). Copper histidinate is not an inducer of CYP1A2, CYP2B6, or CYP3A.

Transporter Systems: Copper histidinate is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OAT1B3, or OCT2. Copper histidinate is an inhibitor of BSEP and MATE1. Copper histidinate is a weak inhibitor of BCRP, MATE2K, OCT1, and OCT2. Copper histidinate is not an inhibitor of P-gp, OAT1, OAT3, OATP1B1, or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal studies to evaluate the carcinogenic potential of copper histidinate have not been conducted with ZYCUBO.

Mutagenesis

ZYCUBO was not mutagenic or clastogenic in a standard battery of genotoxicity tests [bacterial mutagenicity (Ames), micronucleus assay in TK6 cells *(in vitro)*, and rat bone marrow micronucleus assay *(in vivo)]*.

Impairment of Fertility

Animal studies to evaluate effects of copper histidinate on fertility and early embryonic development have not been conducted with ZYCUBO.

14 CLINICAL STUDIES

The efficacy of ZYCUBO was evaluated in pediatric patients with Menkes disease (age at

treatment initiation ranges 0.1 to 31.4 months) receiving 3 years of copper histidinate treatment in two open-label, single-arm clinical trials (Trial 1, NCT00001262 and Trial 2, NCT00811785). 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.
- 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 as described in Table 2.

Table 2. Patient Cohorts in the Pooled Efficacy Population

	Treated Cohorts		**Untreated Cohorts**	
	ZYCUBO-Early Treatment (ZYCUBO-ET) n=31	**ZYCUBO-Late Treatment (ZYCUBO-LT) n=35**	**External Control-Early Treatment (EC-ET) n=17**	**External Control-Late Treatment (EC-LT) n=16**
Eligibility	Started ZYCUBO treatment within 4 weeks of birth [1]	Started ZYCUBO treatment after 4 weeks of birth [2]	• No prior ZYCUBO or copper treatment • Asymptomatic for significant neurological signs and symptoms approximately 4 weeks after birth • Survived at least 4 weeks after diagnosis	• Subset of the EC-ET cohort • Diagnosed with Menkes disease after 4 weeks of birth • Survived at least 2 weeks after diagnosis
Age at diagnosis (months)	0.1 (-4.5 – 1.9)	4.8 (0.4 – 29.4)	4.7 (2.1 – 22.2)	5.6 (2.1 – 22.2)
Age at treatment initiation (months)	0.4 (0.1 – 1.9)	7.1 (1.3 – 31.4)	NA	NA
Treatment	34.1 (1.1 – 36)	20 (1.3 – 36)	NA	NA

duration (months)				

All values are in median (range)

[1] Within 4 weeks of birth or within 4 weeks of birth corrected for prematurity (i.e., < 40 weeks' gestation)

[2] After 4 weeks of birth or after 4 weeks of birth corrected for prematurity (i.e., < 40 weeks' gestation)

In the 4 cohorts, 81 patients were male (98%) except for 2 female (2%) patients in ZYCUBO-LT. The pooled efficacy population included patients with the following race and ethnicity: 52 White (63%), 11 Hispanic (13%), 8 Black or African American (10%), 6 Unknown (7%), 4 Other (5%), and 2 Asian or Pacific Islander (2%). The majority of patients in all 4 cohorts were born prematurely: ZYCUBO-ET = 77%, ZYCUBO-LT = 66%, EC-ET = 82%, and EC-LT = 81%.

Efficacy Results

Primary Efficacy Results (Overall Survival) in the ZYCUBO-ET and EC-ET Cohorts

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 (Table 3 and Figure 1).

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.

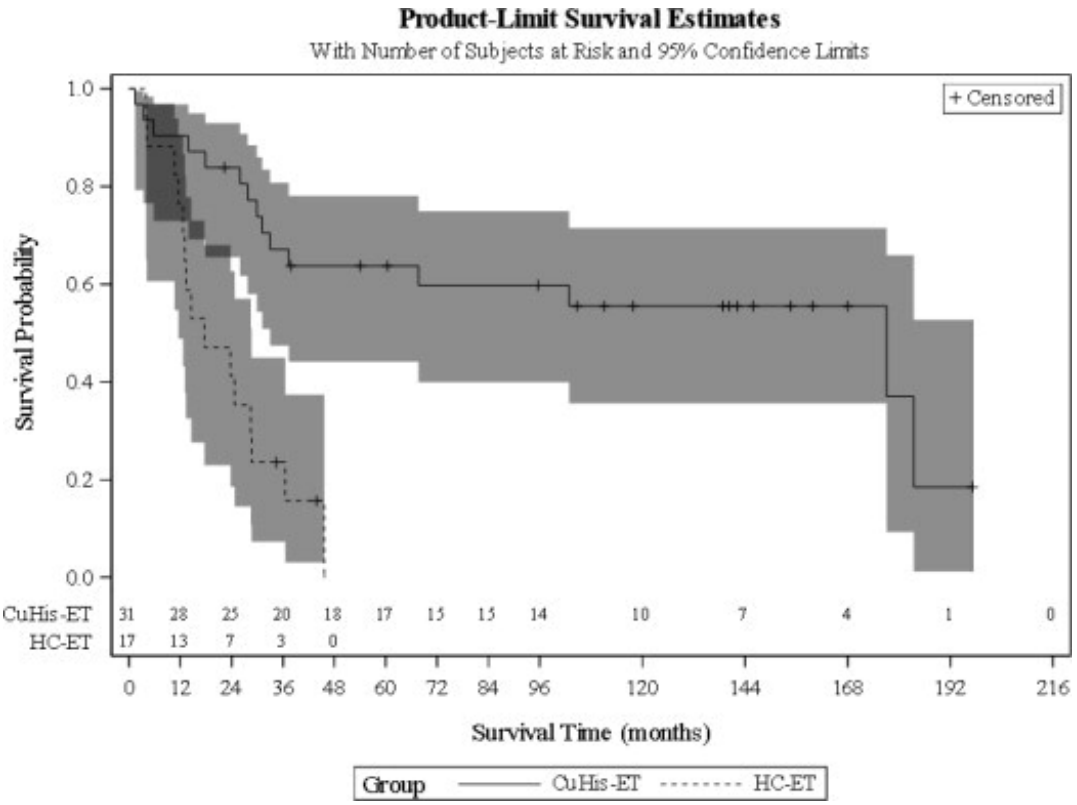
Table 3. Primary Efficacy Results: Overall Survival in ZYCUBO Early Treatment and External Control Early Treatment Cohorts with Menkes Disease

	ZYCUBO-Early Treatment (n=31)	**External Control-Early Treatment (n=17)**
Number (%) of Patients Alive	16 (52%)	2 (12%)
Median survival time (months) (95% CI)	177.1 (33, NE)	17.6 (11.5, 28.6)
Hazard Ratio (95% CI)	0.22 (0.10, 0.49)	

CI=Confidence Interval; NE=Not estimable

Note: If death dates were unknown, patients were censored at the last known date alive.

Figure 1. Kaplan-Meier Overall Survival Curve for the ZYCUBO Early Treatment and External Control Early Treatment Cohorts with Menkes Disease



CuHis=copper histidinate; ET=early treatment; EC=external control

Secondary Efficacy Results (Overall Survival) in the ZYCUBO-LT and EC-LT Cohorts

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 (Table 4 and Figure 2).

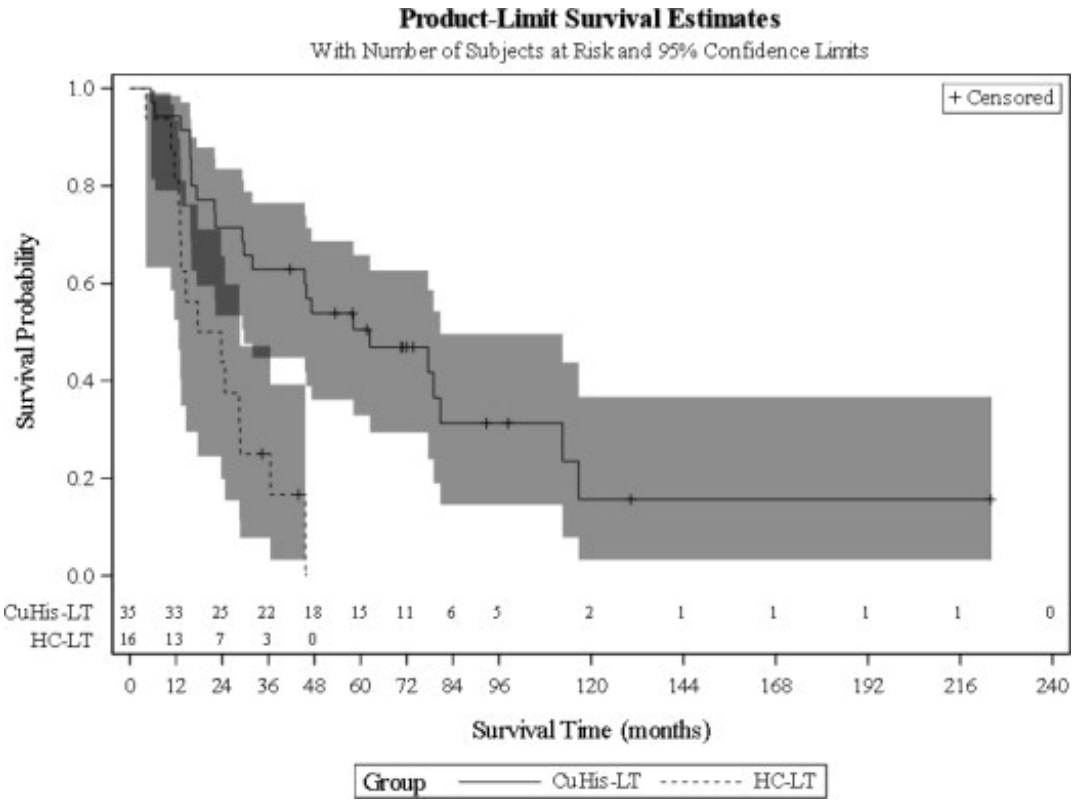
Table 4. Secondary Efficacy Results: Overall Survival in ZYCUBO Late Treatment and External Control Late Treatment Cohorts with Menkes Disease

	ZYCUBO Late-Treatment (LT) (n=35)	**External Control-Late Treatment (EC-LT) (n=16)**
Number of Patients Alive (%)	12 (34%)	2 (12%)
Median survival time (months) (95% CI)	62.4 (29.6, 80.7)	20.7 (12.6, 28.6)
Hazard Ratio (95% CI)	0.27 (0.12, 0.57)	

CI=Confidence Interval

Note: If death dates were unknown, patients were censored at the last known date alive.

Figure 2. Kaplan-Meier Overall Survival Curve for ZYCUBO Late Treatment and External Control Late Treatment Cohorts with Menkes Disease



CuHis=copper histidinate; LT=late treatment; EC=external control

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZYCUBO (copper histidinate) for injection is supplied as a sterile, preservative-free, blue lyophilized powder or cake in a single-dose vial. Each vial contains 2.9 mg of copper histidinate (equivalent to 0.5 mg elemental copper). ZYCUBO is available as:

- One 2.9 mg single-dose vial in a carton: NDC 42358-329-01

Storage and Handling

Store ZYCUBO vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton.

Store ZYCUBO reconstituted solution either refrigerated or at controlled room temperature *[see Dosage and Administration (2.5)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Instructions for Use).

Drug-Induced Kidney Injury, Liver Dysfunction, and Hematological Abnormalities

Advise the patient and/or caregiver of the potential for the patient to experience drug-induced kidney injury, liver dysfunction, and hematological abnormalities. *[see Warnings and Precautions (5.1)]*.

Manufactured by:
Zydus Lifesciences Ltd.
Vadodara 391510
India

Manufactured for:
Sentynl Therapeutics, Inc.
Solana Beach, CA 92075

ZYCUBO is a registered trademark of Sentynl Therapeutics, Inc.

INSTRUCTIONS FOR USE

ZYCUBO® [zye kyoo boe]

(copper histidinate)

for injection, for subcutaneous use

This Instructions for Use contains information on how to prepare and inject ZYCUBO. Read this Instructions for Use before you prepare and inject a dose of ZYCUBO for the first time and each time you get a ZYCUBO refill. There may be new information. This information does not take the place of talking to your healthcare provider about your child's medical condition or their treatment.

ZYCUBO is for subcutaneous injection only (inject directly under the skin). Always follow the specific instructions given by your healthcare provider.

- If you have questions about preparing or injecting ZYCUBO, call SentynlCares | ZYCUBO Patient Support Services at 1-888-251-2800.

Important information you need to know before preparing and injecting ZYCUBO:

- Your healthcare provider should show you the right way to prepare and inject your child's prescribed dose of ZYCUBO before you do this for the first time.
- Your healthcare provider will prescribe the amount of ZYCUBO needed for each dose for your child. Confirm the amount of ZYCUBO needed at each visit with your child's healthcare provider.
- ZYCUBO comes as a powder or cake in a vial. Each vial of ZYCUBO must be mixed with 0.9% sodium chloride to mix (dissolve) the powder or cake before use.
- **Do not mix ZYCUBO with anything other than 0.9% sodium chloride.**
- Vials of ZYCUBO are for 1 time use only. Throw the vial away after use, even if there is medicine left in the vial. **Do not** save for later use. Throw away used vials in your household trash.
- **If your child misses a dose of ZYCUBO, inject the dose as soon as possible. Inject the next scheduled dose at least 6 hours after you finish injecting the missed dose.**
- **Do not** expose ZYCUBO to any heat source, such as a microwave or hot water.
- **Do not** share needles and syringes. See Step 13: **“Throw away (dispose of) used needles and syringes.”**

Storing ZYCUBO and other supplies:

Vials of ZYCUBO **before mixing**:

- Store ZYCUBO in the **refrigerator** between 36°F to 46°F (2°C to 8°C).

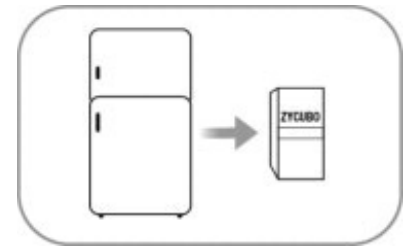
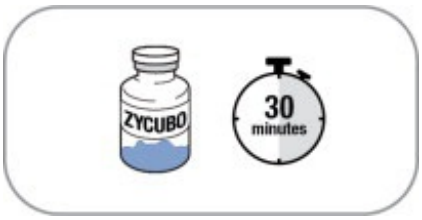
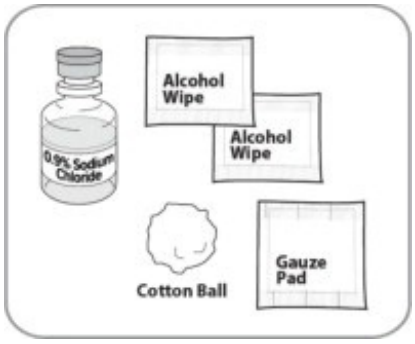
- Keep ZYCUBO vials in the **original carton** until you are ready to use it.

Vials of ZYCUBO **after mixing**:
- If you do not use the ZYCUBO solution right away after mixing, store the mixed ZYCUBO vial:
  - **in the refrigerator between 36°F to 46°F (2°C to 8°C) and use within 24 hours.** Throw away (discard) the mixed ZYCUBO vial if not used within 24 hours.
  - **at room temperature between 68°F to 77°F (20°C to 25°C) and use within 4 hours.** Throw away (discard) the mixed ZYCUBO vial if not used within 4 hours.
- Write the date and time you mixed ZYCUBO with 0.9% sodium chloride on the carton.
- **Do not shake** ZYCUBO after it has been mixed.

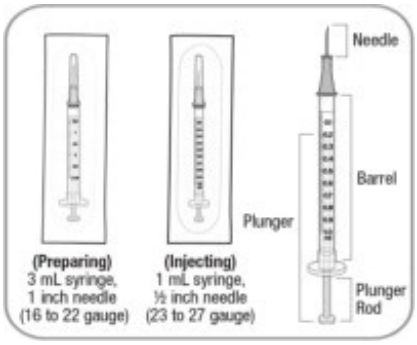
Other supplies:
- Store other supplies according to the manufacturer instructions (see Step 2: "**Gather and check other supplies**" for a list of supplies needed).

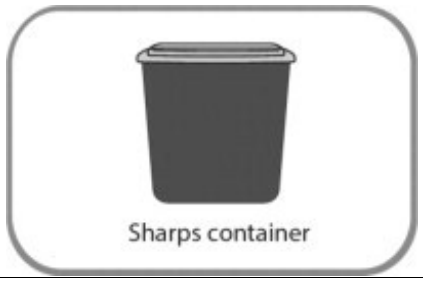
Keep ZYCUBO and all medicines out of the reach of children.

Preparing and injecting ZYCUBO

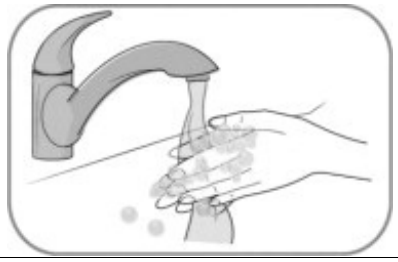
Step 1: Gather and check ZYCUBO vial for damage and expiration date a) Remove the ZYCUBO carton from the refrigerator. Remove the ZYCUBO vial from the carton. b) Check the ZYCUBO vial for damage and the expiration date. • **Do not** use the vial and contact the healthcare provider if the vial is damaged, expired or the flip-off cap on the vial is broken or missing. c) Allow the ZYCUBO vial to sit at room temperature for about 30 minutes.	 
Step 2: Gather and check other supplies • 1 vial of 0.9% sodium chloride ◦ Check the expiration date on the vial. ◦ **Do not** use the vial if the expiration date has passed. ◦ **Do not** use the vial if the flip-off cap on the vial is broken or missing. • One (1) sterile, 3 mL syringe with 1 inch needle (16 to 22 gauge) for preparing ZYCUBO	

- One (1) sterile, 1 mL syringe with 1/2 inch needle (23 to 27 gauge) for injecting ZYCUBO.
  - Check the expiration dates of both sterile syringes with sterile needles.
  - **Do not** use if the expiration date has passed.
  - **Do not** use if the packaging is damaged.
- Alcohol wipes
- Gauze pads or Cotton ball
- 1 sharps disposal container (see Step 13: **"Throw away (dispose of) used needles and syringes"**)
- Gloves (if instructed by your healthcare provider)



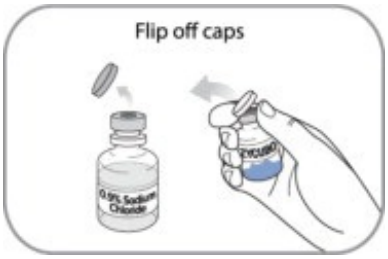


Step 3: Wash your hands
If you have been told to wear gloves to prepare and inject ZYCUBO, put them on now.



Step 4: Prepare the vials

a) Remove the flip-off cap from the sodium chloride vial and ZYCUBO vial.
b) Throw away (discard) the vial caps in the trash.



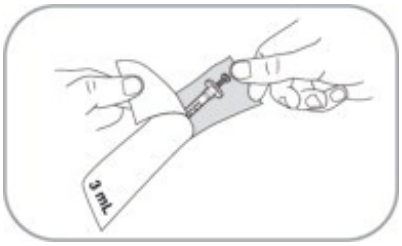
c) Clean the rubber stopper of each vial with an alcohol wipe and allow to air dry.
   - **Do not** blow on the stopper to dry it faster.

Note: If you touch the rubber stopper, clean it again with a new alcohol wipe.

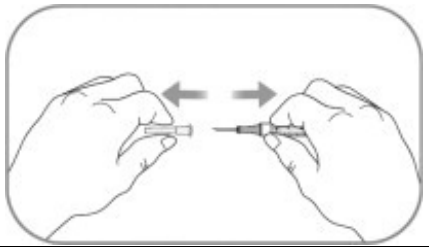
Step 5: Prepare the syringe used for

withdrawing sodium chloride

a) Remove a 3 mL syringe with needle from the plastic packaging.

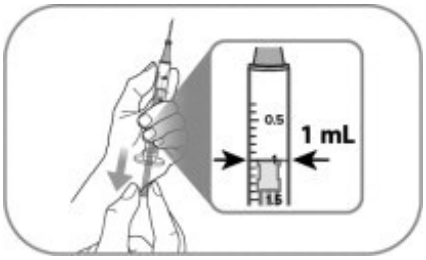


b) Pull the needle cover straight off and throw it away in the trash.
   - **Do not** touch the needle or let the needle touch any surface.



Step 6: Withdraw 1 mL of sodium chloride into syringe

a) Hold the syringe barrel with one hand. With your other hand, draw air into the syringe by pulling back on the plunger rod until the top of the plunger lines up with the 1 mL mark on the syringe.



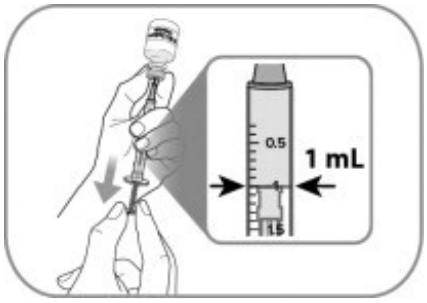
b) Hold the sodium chloride vial on a clean, flat work surface and insert the needle into the center of the sodium chloride vial stopper.
   Note: If you remove the needle at any point, clean the rubber stopper with a new alcohol wipe before reinserting the needle.

c) Turn the vial upside down.

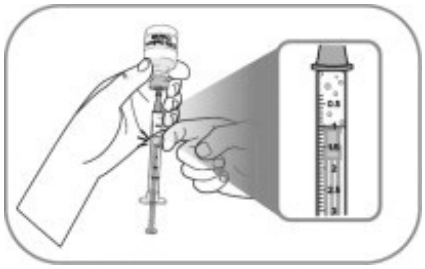
d) Slowly push up on the plunger rod to push all the air from the syringe into the vial.

e) Make sure the tip of the needle is in the

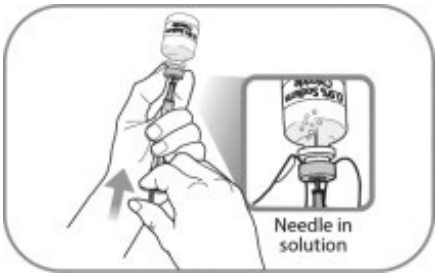
sodium chloride solution. Slowly pull down on the plunger rod of the syringe until the top of the plunger reaches the 1 mL mark on the syringe.



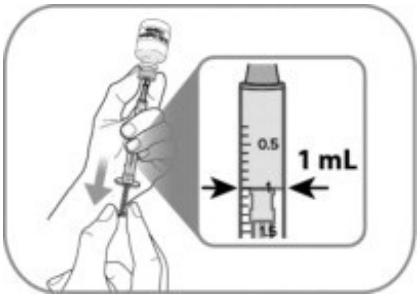
f) Gently tap the syringe barrel to remove as many air bubbles as possible. It is acceptable if some air bubbles remain in the syringe after you tap the syringe.



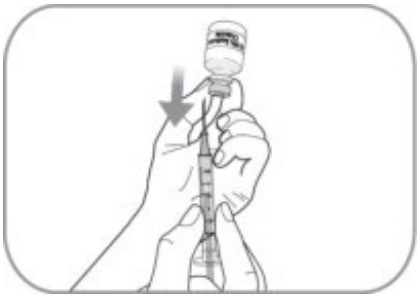
- Push the plunger rod up to remove as many large air bubbles as you can.



g) Check to make sure that 1 mL of sodium chloride has been withdrawn into the syringe. If the amount is less than 1 mL, repeat **Steps 6e** and **6f** until you have 1 mL of sodium chloride.

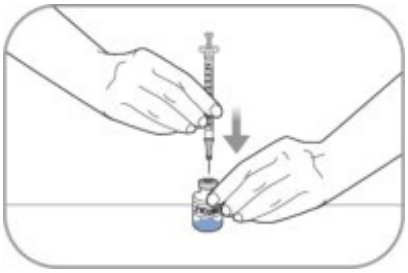


h) Remove the needle and syringe from the sodium chloride vial. Be careful not to move the plunger.



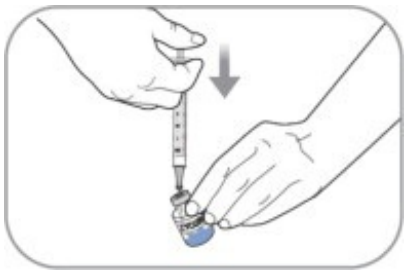
Step 7: Mix ZYCUBO until dissolved

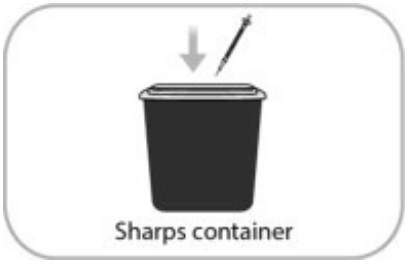
a) Hold the ZYCUBO vial on a clean, flat work surface.
b) Insert the syringe with 1 mL of sodium chloride into the center of the ZYCUBO vial stopper.
c) Tilt the vial so that the tip of the needle is pointing toward the inside wall of the vial.



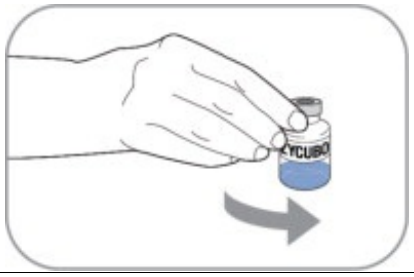
- With your thumb, slowly push the plunger rod down all the way. The liquid should go down the inside wall of the vial.

d) Carefully remove the needle from the vial. Throw away (dispose of) the used needle and syringe in your sharps disposal container right away.
   - **Do not** try to recap the needle.See Step 13: **"Throw away (dispose of) used needles and syringes."**





e) Gently swirl the vial continuously until the powder is completely dissolved. **Do not** shake the vial.

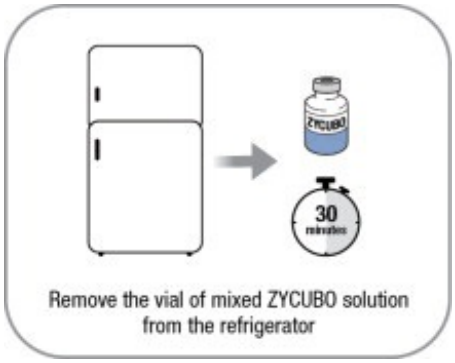


Step 8: Check solution
Check that the ZYCUBO solution is a blue color.
- **Do not** use if the mixed solution is not a blue color, is cloudy, or contains particles. Ask your pharmacist for a replacement vial.

Step 9: Determine the injection time

After mixing, inject the ZYCUBO solution right away or inject the ZYCUBO solution:

- within **24 hours if stored in the refrigerator.** Throw away (discard) the mixed ZYCUBO vial if not used within 24 hours.
  - If you store the mixed ZYCUBO vial in the refrigerator, remove the vial from the refrigerator and allow it to sit at room temperature for about 30 minutes.
- within **4 hours if stored at room temperature.** Throw away (discard) the mixed ZYCUBO vial if not used within 4 hours.
- If you do not inject the ZYCUBO solution right away:
  - Wash your hands well with soap and water.

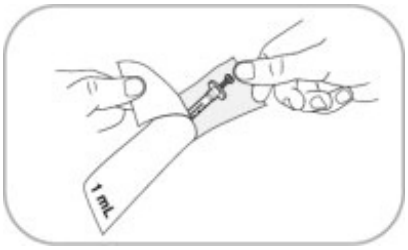


Remove the vial of mixed ZYCUBO solution from the refrigerator

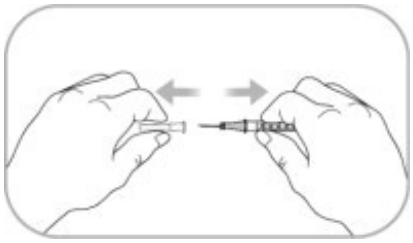
  - Wipe the rubber stopper of the mixed ZYCUBO vial with a new alcohol wipe and allow to air dry.
    - **Do not** blow on the rubber stopper to dry faster.

Step 10: Prepare a syringe with the prescribed dose of ZYCUBO

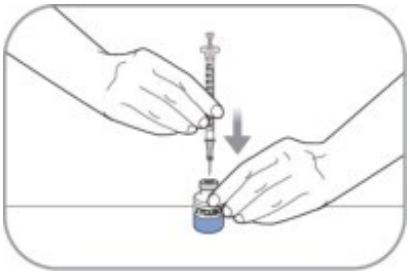
a) Remove a 1 mL syringe with needle from the plastic packaging.



b) Pull the needle cover straight off and throw it away in the trash.
   - **Do not** touch the needle or let the needle touch any surface.

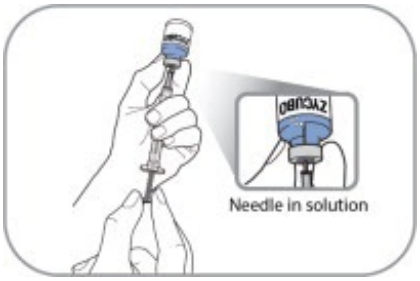


c) Hold the mixed ZYCUBO vial on a clean, flat work surface and insert the needle into the center of the ZYCUBO vial stopper.
Note: If you remove the needle at any point, clean the rubber stopper with a new alcohol wipe before reinserting the needle.

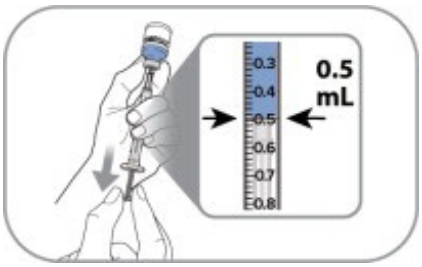


d) Turn the vial upside down.

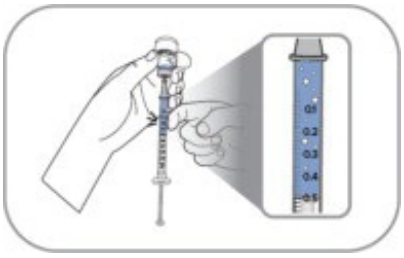
e) Move the needle so that the tip is in the ZYCUBO solution.



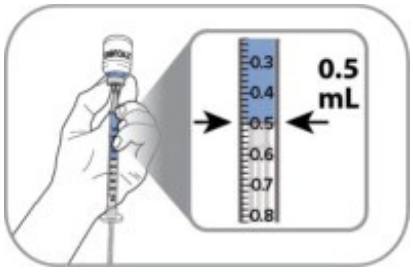
f) Slowly pull back on the plunger rod to fill the syringe with 0.5 mL of ZYCUBO solution. The top of the plunger should line up with the 0.5 mL mark on the syringe.



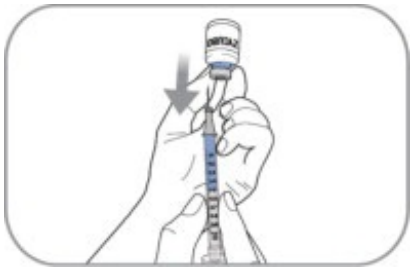
g) Gently tap the syringe barrel to remove as many air bubbles as possible. It is acceptable if some air bubbles remain in the syringe after you tap the syringe.
- Push the plunger rod up to remove as many large air bubbles as you can.



h) Check to make sure that 0.5 mL of ZYCUBO solution has been withdrawn into the syringe. If the amount is less than 0.5 mL, repeat **Steps 10f** and **10g** until you have 0.5 mL of ZYCUBO solution.



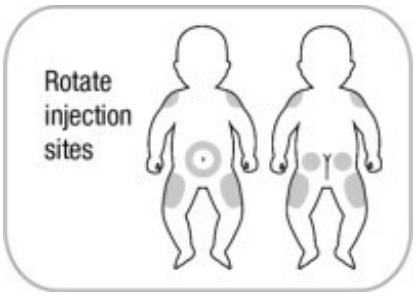
i) Remove the needle and syringe from the ZYCUBO vial.



j) Throw away the used ZYCUBO vial in your household trash after use, even if there is medicine left in the vial.

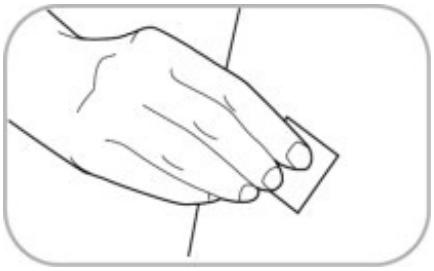
Step 11: Prepare the injection site
ZYCUBO is injected under the skin (subcutaneously).

a) Choose one (1) of the following injection sites:
   - stomach area (abdominal area), 2 inches from belly button,
   - buttocks, **or**
   - outer area of the upper arm or thigh.



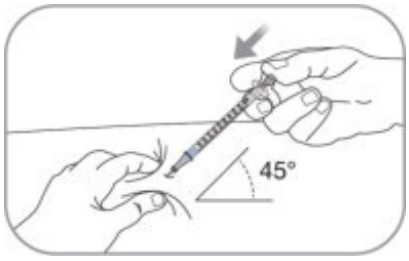
- Change (rotate) the injection site with each injection to reduce your risk of skin problems.
- **Do not** give injections into areas where the skin is scarred, tender, bruised, red or hard.

b) Clean the injection site with a new alcohol wipe.
c) Let the injection site air dry.
   - **Do not** touch, wipe, fan, or blow on it.



Step 12: Inject ZYCUBO

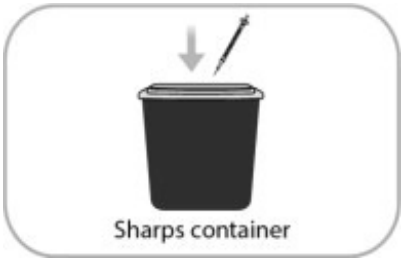
a) Pinch the skin around the clean injection site with one hand. With the other hand, hold the syringe and fully insert the needle into the skin at a 45-degree angle. **Do not** press the plunger rod until you are ready to inject.
b) Push the plunger rod all the way down to inject all of the ZYCUBO solution.
c) Remove the needle from the injection site at the same 45-degree angle it was inserted.
   - If you see any blood, lightly press a cotton ball or gauze at the injection site. Apply an adhesive bandage if



necessary. **Do not** rub the injection site.
- If the injection site becomes red or sore, call your healthcare provider right away.

Step 13: Throw away (dispose of) used needles and syringes

- Put your used needles and syringes in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) needles and syringes in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: https://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- Keep the sharps disposal container out of the reach of children.



If you have questions about preparing or injecting ZYCUBO, call SentynlCares | ZYCUBO Patient Support Services at 1-888-251-2800.

Manufactured by: Zydus Lifesciences Ltd., Vadodara – 391510, India
Manufactured for: Sentynl Therapeutics, Inc., Solana Beach, CA 92075
This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Issued: 1/2026

Principal Display Panel - 2.9 mg Carton Label

NDC 42358-329-01

Zycubo ®
(copper histidinate) for injection

2.9 mg/vial

For subcutaneous injection

One Single-Dose vial

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

Rx only

Principal Display Panel - 2.9 mg Vial Label

NDC 42358-329-01 Rx only

Zycubo ®
(copper histidinate) for injection

2.9 mg/vial

For subcutaneous injection

One Single-Dose vial

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

ZYCUBO
copper histidinate injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42358-329
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
copper histidinate (UNII: 9078K3MO9U) (copper histidinate - UNII:9078K3MO9U)	copper histidinate	2.9 mg

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:42358-329-01	1 in 1 CARTON	02/25/2026	
1		1 in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA211241	01/12/2026	

Labeler - Sentynl Therapeutics, Inc. (078313706)

Revised: 1/2026 Sentynl Therapeutics, Inc.