

Important Update Regarding Cycloserine

Cycloserine is an important medicine used for the treatment of multiple-drug-resistant tuberculosis. It is estimated that approximately 100 patients per year are diagnosed with multi- drug-resistant tuberculosis in the United States and a fraction of those patients receive Cycloserine as part of their treatment regimen.

In trying to support the product, the manufacturer, The Chao Center, was losing significant money. Rodelis Therapeutics acquired Cycloserine from The Chao Center on August 19, 2015, with the commitment to continue investing resources to ensure the long-term availability of the product. The agreement was a partnership whereby The Chao Center would continue to manufacture Cycloserine and Rodelis would provide commercial support.

Rodelis was putting in place a patient-assistance program where uninsured patients, which are a significant portion of the patient base, would apply to receive Cycloserine at no cost.

Along with ensuring Cycloserine's long-term availability, Rodelis planned to invest resources to help patients stay on the medication, to explore additional dosage and delivery methods to help patients tolerate the medicine, and to investigate other possible uses.

Rodelis Therapeutics and The Chao Center mutually agreed last week that it is in the best interests of the patients to return the rights of Cycloserine to The Chao Center. Rodelis Therapeutics, which is a privately-held company, remains committed to developing and investing in therapeutics of orphan diseases and high unmet medical needs.

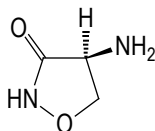
CYCLOSERINE

CAPSULES, USP

DESCRIPTION

Cycloserine, (*R*)-4-amino-3-isoxazolidinone, is a broad-spectrum antibiotic that is produced by a strain of *Streptomyces orchidaceus* and has also been synthesized. Cycloserine is a white to off-white powder that is soluble in water and stable in alkaline solution. It is rapidly destroyed at a neutral or acid pH.

Cycloserine has a pH between 5.5 and 6.5 in a solution containing 100 mg/mL. The molecular weight of cycloserine is 102.09, and it has an empirical formula of $C_4H_6NO_2$. The structural formula of cycloserine is as follows:



Each capsule contains cycloserine, 250 mg (2.45 mmol); D & C Yellow No. 10, F D & C Blue No. 1, F D & C Red No. 3, F D & C Yellow No. 6, gelatin, iron oxide, talc, titanium dioxide, and other inactive ingredients.

— CLINICAL PHARMACOLOGY —

After oral administration, cycloserine is readily absorbed from the gastrointestinal tract, with peak blood levels occurring in 4 to 8 hours. Blood levels of 25 to 30 mg/mL can generally be maintained with the usual dosage of 250 mg twice a day, although the relationship of plasma levels to dosage is not always consistent. Concentrations in the cerebrospinal fluid, pleural fluid, fetal blood, and mother's milk approach those found in the serum. Detectable amounts are found in ascitic fluid, bile, sputum, amniotic fluid, and lung and lymph tissues. Approximately 65% of a single dose of cycloserine can be recovered in the urine within 72 hours after oral administration. The remaining 35% is apparently metabolized to unknown substances. The maximum excretion rate occurs 2 to 6 hours after administration, with 50% of the drug eliminated in 12 hours.

Microbiology: Cycloserine inhibits cell-wall synthesis in susceptible strains of gram-positive and gram-negative bacteria and in *Mycobacterium tuberculosis*.

Susceptibility Tests: Cycloserine clinical laboratory standard powder is available for both direct and indirect methods¹ of determining the susceptibility of strains of mycobacteria. Cycloserine MICs for susceptible strains are 25 µg/mL or lower.

— INDICATIONS AND USAGE —

Cycloserine is indicated in the treatment of active pulmonary and extrapulmonary tuberculosis (including renal disease) when the causative organisms are susceptible to this drug and when treatment with the primary medications (streptomycin, isoniazid, rifampin, and ethambutol) has proved inadequate. Like all antituberculosis drugs, cycloserine should be administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent.

Cycloserine may be effective in the treatment of acute urinary tract infections caused by susceptible strains of gram-positive and gram-negative bacteria, especially *Enterobacter* spp. and *Escherichia coli*. It is generally no more and is usually less effective than other antimicrobial agents in the treatment of urinary tract infections caused by bacteria other than mycobacteria. Use of cycloserine in these infections should be considered only when more conventional therapy has failed and when the organism has been demonstrated to be susceptible to the drug.

— CONTRAINDICATIONS —

Administration is contraindicated in patients with any of the following:

- Hypersensitivity to cycloserine
- Epilepsy
- Depression, severe anxiety, or psychosis
- Severe renal insufficiency
- Excessive concurrent use of alcohol

— WARNINGS —

Administration of cycloserine should be discontinued or the dosage reduced if the patient develops allergic dermatitis or symptoms of CNS toxicity, such as convulsions, psychosis, somnolence, depression, confusion, hyperreflexia, headache, tremor, vertigo, paresis, or dysarthria.

The toxicity of cycloserine is closely related to excessive blood levels (above 30 µg/mL), as determined by high dosage or inadequate renal clearance. The ratio of toxic dose to effective dose in tuberculosis is small.

The risk of convulsions is increased in chronic alcoholics.

Patients should be monitored by hematologic, renal excretion, blood level, and liver function studies.

— PRECAUTIONS —

General: Before treatment with cycloserine is initiated, cultures should be taken and the organism's susceptibility to the drug should be established. In tuberculous infections, the organism's susceptibility to the other antituberculosis agents in the regimen should also be demonstrated.

Anticonvulsant drugs or sedatives may be effective in controlling symptoms of CNS toxicity, such as convulsions, anxiety, and tremor. Patients receiving more than 500 mg of cycloserine daily should be closely observed for such symptoms. The value of pyridoxine in preventing CNS toxicity from cycloserine has not been proved.

Administration of cycloserine and other antituberculosis drugs has been associated in a few instances with vitamin B₁₂ and/or folic-acid deficiency, megaloblastic anemia, and sideroblastic anemia. If evidence of anemia develops during treatment, appropriate studies and therapy should be instituted.

Laboratory Tests: Blood levels should be determined at least weekly for patients with reduced renal function, for individuals receiving a daily dosage of more than 500 mg, and for those showing signs and symptoms suggestive of toxicity. The dosage should be adjusted to keep the blood level below 30 µg/mL.

Drug Interactions: Concurrent administration of ethionamide has been reported to potentiate neurotoxic side effects.

Alcohol and cycloserine are incompatible, especially during a regimen calling for large doses of the latter. Alcohol increases the possibility and risk of epileptic episodes.

Concurrent administration of isoniazid may result in increased incidence of CNS effects, such as dizziness or drowsiness. Dosage adjustments may be necessary

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and patients should be monitored closely for signs of CNS toxicity.

Carcinogenesis, Mutagenicity, and Impairment of Fertility: Studies have not been performed to determine potential for carcinogenicity. The Ames test and unscheduled DNA repair test were negative. A study in 2 generations of rats showed no impairment of fertility relative to controls for the first mating but somewhat lower fertility in the second mating.

Pregnancy Category C: A study in 2 generations of rats given doses up to 100 mg/kg/day demonstrated no teratogenic effect in offspring. It is not known whether cycloserine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cycloserine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from cycloserine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Usage in Pediatric Patients: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Most adverse reactions occurring during therapy with cycloserine involve the nervous system or are manifestations of drug hypersensitivity. The following side effects have been observed in patients receiving cycloserine:

Nervous system symptoms (which appear to be related to higher dosages of the drug, i.e., more than 500 mg daily)

- Convulsions
- Drowsiness and somnolence
- Headache
- Tremor
- Dysarthria
- Vertigo
- Confusion and disorientation with loss of memory
- Psychoses, possibly with suicidal tendencies
- Character changes
- Hyperirritability
- Aggression
- Paresis
- Hyperreflexia
- Paresthesia
- Major & minor (localized) clonic seizures
- Coma

Cardiovascular: Sudden development of congestive heart failure in patients receiving 1 to 1.5 g of cycloserine daily has been reported

Allergy (apparently not related to dosage)

Skin rash

Miscellaneous: Elevated serum transaminase, especially in patients with preexisting liver disease

OVERDOSAGE

Signs and Symptoms: Acute toxicity from cycloserine can occur if more than 1 g is ingested by an adult. Chronic toxicity from cycloserine is dose related and can occur if more than 500 mg is administered daily. Patients with renal impairment will accumulate cycloserine and may develop toxicity if the dosing regimen is not modified. Patients with severe renal impairment should not receive the drug. The central nervous system is the most common organ system involved with toxicity. Toxic effects may include headache, vertigo, confusion, drowsiness, hyperirritability, paresthesias, dysarthria, and psychosis. Following larger ingestions, paresis, convulsions, and coma often occur. Ethyl alcohol may increase the risk of seizures in patients receiving cycloserine.

The oral median lethal dose in mice is 5290 mg/kg.

Treatment: To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physician's Desk Reference (PDR)*. In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Overdoses of cycloserine have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider

charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

In adults, many of the neurotoxic effects of cycloserine can be both treated and prevented with the administration of 200 to 300 mg of pyridoxine daily.

The use of hemodialysis has been shown to remove cycloserine from the bloodstream. This procedure should be reserved for patients with life-threatening toxicity that is unresponsive to less invasive therapy.

DOSAGE AND ADMINISTRATION

Cycloserine is effective orally and is currently administered only by this route. The usual dosage is 500 mg to 1 g daily in divided doses monitored by blood levels.² The initial adult dosage most frequently given is 250 mg twice daily at 12-hour intervals for the first 2 weeks. A daily dosage of 1 g should not be exceeded.

HOW SUPPLIED

Cycloserine is available as a 250 mg capsule with an opaque red cap and opaque gray body imprinted with "CHAO" and "F04" in edible black ink on both the cap and the body.

Aluminum blisters (a pack of 3 cards each with 10 capsules). NDC 13845-1202-2.

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

REFERENCES

1. Kubica GP, Dye WE: Laboratory methods for clinical and public health — mycobacteriology. US Department of Health, Education and Welfare, Public Health Service, 1967, pp 47–55, 66–70.
2. Jones LR: Colorimetric determination of cycloserine, a new antibiotic. *Anal Chem* 1956; 28:39.

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Literature revised
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