

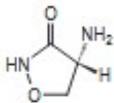
CYCLOSERINE- cycloserine capsule
Parsolex Gmp Center, Inc.

Cycloserine Capsules, USP, 250 mg, Blister Pack × 30

DESCRIPTION

D -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 $C_3H_6N_2O_2$. 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, and titanium dioxide.

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 $\mu\text{g/mL}$ 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, urine, 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.

Mechanism of Action: The antibacterial activity of Cycloserine results from inhibition of cell-wall synthesis in susceptible strains of gram-positive and gram-negative bacteria.

Antibacterial Activity: Cycloserine has been shown to be active against most isolates of the following microorganism, both in vitro and in clinical infections [see Indications and Usage]: Mycobacterium tuberculosis.

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. 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 B 12 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 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: There are no adequate and well-controlled studies with the use of Cycloserine in pregnant women. A study in 2 generations of rats given doses up to 100 mg/kg/day (approximately equivalent to the maximum recommended human dose

on a body surface area basis) demonstrated no teratogenic effect in offspring. Cycloserine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Geriatric Use: Clinical studies of cycloserine did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. The toxicity of cycloserine is closely related to excessive blood levels (above 30 µg/mL) as determined by high dosage or inadequate renal clearance (see WARNINGS). 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 (see PRECAUTIONS, Laboratory Tests).

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. The central nervous system is the most common organ system involved with toxicity. Toxic effects may include headache, vertigo, confusion, drowsiness, hyperirritability, paresthesias, dysarthria, psychosis paresis, convulsions, and coma.

Treatment: 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.

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 "PGC" 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 Controlled Room Temperature].

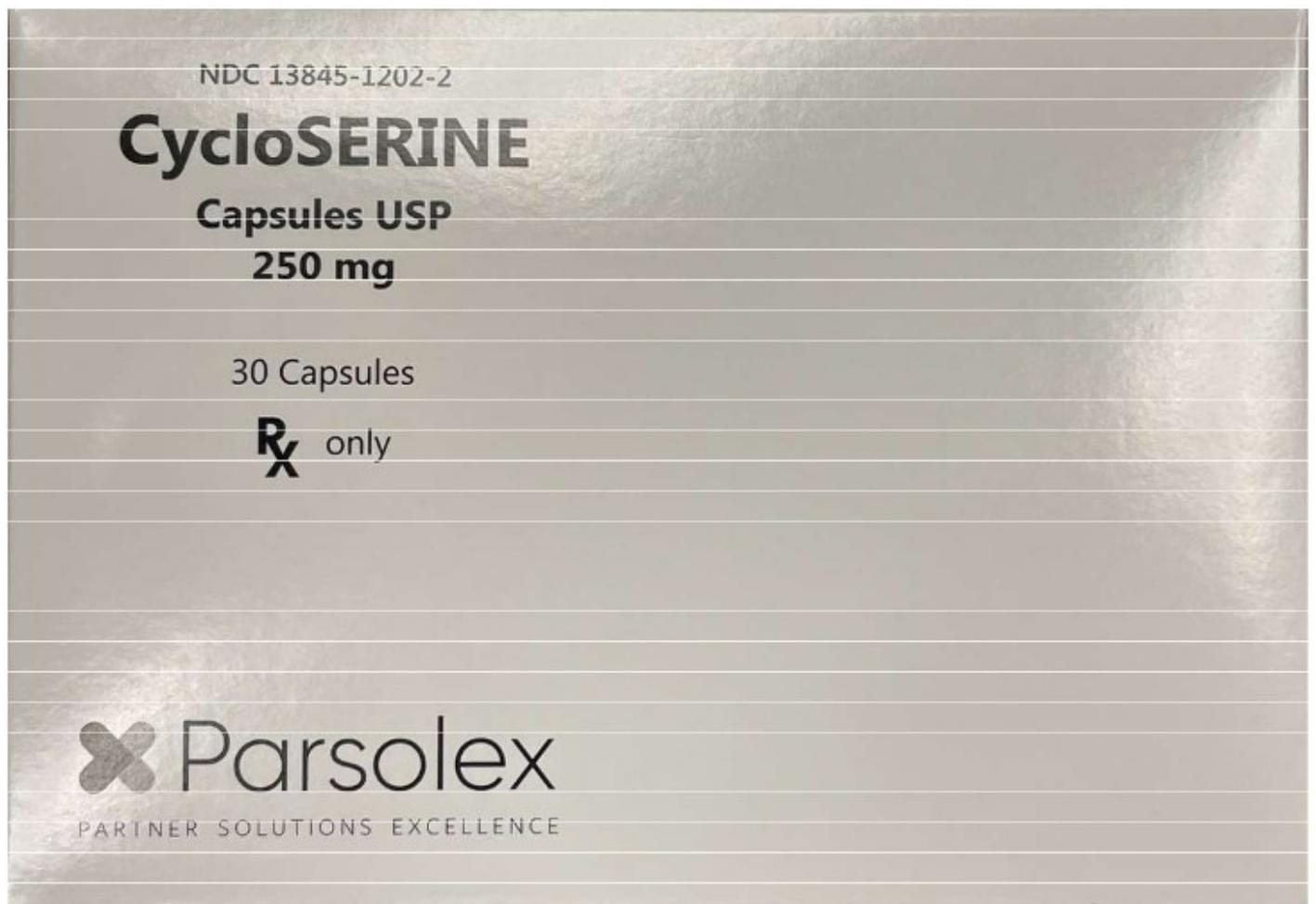
REFERENCES

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.

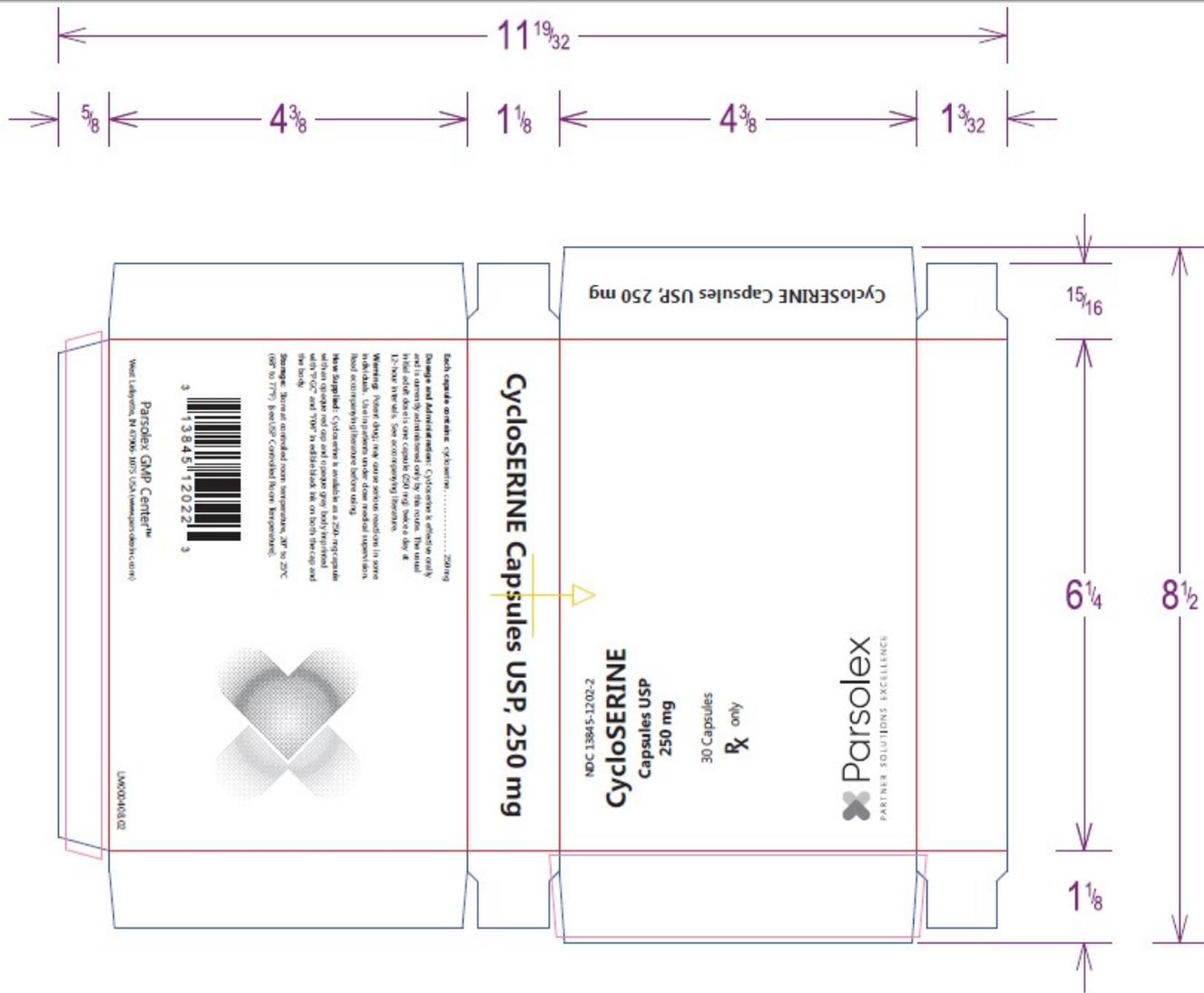
2. Jones LR: Colorimetric determination of cycloserine, a new antibiotic. Anal Chem 1956;28:39.

PACKAGE LABEL DISPLAY

Picture of Carton



Carton Specifications



CYCLOSERINE

cycloserine capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:13845-1202
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CYCLOSERINE (UNII: 95IK5KI84Z) (CYCLOSERINE - UNII:95IK5KI84Z)	CYCLOSERINE	250 mg

Product Characteristics

Color	red (Cap: BOQ - Op. Red 353) , gray (Body: AWZ - Op. Grey 284)	Score	no score
Shape	CAPSULE (Imprint on both cap and body)	Size	20mm
Flavor		Imprint Code	PGC;F04

Contains**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13845-1202-2	3 in 1 CARTON	09/12/2013	
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		



Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA060593	09/12/2013	

Labeler - Parsolex Gmp Center, Inc. (159802532)

Registrant - Parsolex Gmp Center, Inc. (159802532)

Establishment

Name	Address	ID/FEI	Business Operations
Parsolex Gmp Center, Inc.		159802532	manufacture(13845-1202)

Revised: 1/2023

Parsolex Gmp Center, Inc.