

SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.**

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

*https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB330 trade name][†]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 125 mg cycloserine.

Excipients with potential clinical effect

Each capsule contains 0.0018 mg of FD&C yellow #6/ sunset yellow FCF (small amount in capsule shell)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsule

Hard gelatin capsules with an opaque yellow cap and body. They are plain with no markings. They contain white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB330 trade name] is indicated in combination with other antituberculosis agents for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

[TB330 trade name] **must always be given in combination** with other antituberculosis agents.

Adults

The recommended dose is 10-15 mg/kg/day, up to a maximum dose of 1000 mg/day, given in two divided doses every 12 hours or once a day if tolerated.

In practice, the following dose of [TB330 trade name] may be given:

Body weight	Daily dose	Number of mini capsules daily
46 kg or more	750 mg	6*

*An alternative formulation supplying 250 mg of cycloserine may be preferred to reduce the number of capsules needed

Children and adolescents weighing 30 to less than 46 kg

The recommended dose is 10–15 mg/kg/day given as a single dose or in two divided doses every 12 hours. A daily dose of 1000 mg should not be exceeded.

In practice, the following dose of [TB330 trade name] may be given:

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Body weight	Daily dose	Number of mini capsules daily
30 to less than 46 kg	500 mg	4*

*An alternative formulation supplying 250 mg of cycloserine may be preferred to reduce the number of capsules needed

Children weighing 7 to less than 30 kg

The recommended dose is 15–20 mg/kg/day given as a single dose or in two divided doses every 12 hours. A daily dose of 1000 mg should not be exceeded.

In practice, the following dose of [TB330 trade name] may be given:

Body weight	Daily dose	Number of mini capsules daily
7 to less than 10 kg	125 mg	1
10 to less than 16 kg	250 mg	2
16 to less than 24 kg	375 mg	3
24 to less than 30 kg	500 mg	4*

*An alternative formulation supplying 250 mg of cycloserine may be preferred to reduce the number of capsules needed

Children given a dose of 125 mg should be given it as a single daily dose; if the dose is to be divided in higher weight bands, the health care provider should advise the caregiver on how to divide the dose.

Children weighing 3 to less than 7 kg

For children weighing less than 7 kg, or who are unable to swallow capsules, an extemporaneous preparation may be prepared by dispersing the contents of a 125-mg mini capsule of [TB330 trade name] in 10 mL of drinking water in order to facilitate administration, although bioavailability is uncertain (see section 6.6).

For dosing of infants weighing less than 5 kg an expert in treatment of paediatric drug-resistant tuberculosis should be consulted whenever possible.

Recommended daily doses are as follows:

Body weight	Daily dose	Daily volume of extemporaneous preparation to be taken
3 to less than 5 kg	25 mg	2 mL
5 to less than 7 kg	50 mg	4 mL

For **tuberculous meningitis** different dosing regimens may apply. Current WHO treatment guidelines should be followed.

Therapeutic drug monitoring

If available, therapeutic drug monitoring may be useful. The peak concentration should be kept at <35 µg/mL.

Dose adjustments in adults

Some patients may require alternate day 250 mg and 500 mg dosing to avoid toxicity.

To minimise headaches at the start of therapy, cycloserine can be started at lower doses of 250–500 mg and gradually increased over one to two weeks to achieve the target dose.

Duration of therapy

Therapy should be continued long enough to prevent relapse.

The duration of tuberculosis therapy depends on the regimen chosen, the patient's clinical and radiographical responses, smear and culture results, and susceptibility studies of *Mycobacterium tuberculosis* isolates from the patient or the suspected source case.

If therapy is interrupted, the treatment schedule should be extended to a later completion date depending, e.g. on the length of the interruption, the time during therapy (early or late) or the patient's status.

Special Population

Renal impairment

For patients with creatinine clearance < 30 mL/min or for patients on haemodialysis the recommended dose is 250 mg once daily or 500 mg, 3 times per week. Doses should be given after haemodialysis. Drug concentrations should be monitored to keep peak concentrations <35 µg/mL. Patients should also be carefully monitored clinically for signs of toxicity, and doses should be adjusted accordingly.

Hepatic impairment

Data on cycloserine use in hepatic impairment are scarce. Patients should be carefully monitored for signs of toxicity.

Cycloserine-induced peripheral neuropathy

[TB330 trade name] may be administered concomitantly with pyridoxine. For doses of pyridoxine in the prevention and management of cycloserine toxicity, the product information of relevant pyridoxine products should be consulted (see section 4.4).

Missed doses

It is important to take the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB330 trade name] and reduce its effectiveness. *If a dose is missed at the usual scheduled time in a once-daily regimen then,*

- If more than 12 hours remain until the next scheduled dose, the missed dose should be taken as soon as possible.
- If less than 12 hours remain until the next scheduled dose, the missed dose should be omitted and the regular dosing schedule resumed.

If a dose is missed in a twice-daily (every 12 hours) regimen then,

- If more than 6 hours remain until the next scheduled dose, the missed dose should be taken as soon as possible.
- If less than 6 hours remain until the next scheduled dose, the missed dose should be omitted and the regular dosing schedule resumed.

A double dose should not be taken to make up for a forgotten dose.

Method of administration

Cycloserine should be taken by mouth and preferably on an empty stomach (at least 1 hour before or 2 hours after a meal). It can be taken with orange juice.

See section 6.6 for extemporaneous preparation if a suitable preparation for children is not available.

4.3 Contraindications

Cycloserine is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Epilepsy
- Psychiatric disease (e.g. depression, severe anxiety, psychosis, personality disorders)

- Concurrent use of alcohol and other substance abuse (see section 4.5).

4.4 Special warnings and precautions for use

Before initiation of treatment, bacterial susceptibility to the drug should be established.

Monitoring

Cycloserine peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored regularly during therapy. The peak concentration should be kept below 35 µg/mL.

Patients should also be given blood tests and renal and hepatic function should be monitored.

Neurological and mental function

Neuropsychiatric status should be assessed at least at monthly intervals and more frequently if neuropsychiatric symptoms develop. The most dangerous risk of cycloserine is that of suicide, so mood should be carefully watched and any undue depression or personality change observed should be immediately reported. Monitoring is particularly important when used with delamanid.

Since CNS toxicity is more common with higher doses, patients receiving more than 500 mg daily should be particularly closely observed.

[TB330 trade name] should be discontinued or the dosage reduced if the patient develops symptoms of CNS toxicity, such as convulsions, psychosis, somnolence, depression, confusion, hyperreflexia, headache, tremor, vertigo, paresis, or dysarthria. Anticonvulsant drugs or sedatives may be effective in controlling these symptoms.

Hypersensitivity reactions

The drug should be discontinued if a hypersensitivity reaction (e.g. rash, hepatitis) occurs.

Peripheral neuropathy

The risk of peripheral neuropathy is increased in conditions such as

- malnutrition,
- chronic alcohol dependence,
- HIV infection,
- renal failure,
- diabetes,
- pregnancy or breastfeeding.

[TB330 trade name] should therefore be used with careful monitoring in patients with neuropathy or conditions that may predispose to it. Patients should be encouraged to report signs such as persistent paraesthesia of the hands and feet.

Pyridoxine (vitamin B6) reduces the risk of developing peripheral neuropathy. Individuals with conditions that predispose them to peripheral neuropathy (see above) may be given **pyridoxine supplementation** when taking cycloserine. Treatment doses of pyridoxine may also be used for management if signs of peripheral neuropathy develop.

For doses of pyridoxine, the product information of relevant pyridoxine products should be consulted.

Renal impairment

Cycloserine should be used very cautiously in patients with renal failure (see section 4.2).

Excipients

[TB330 trade name] contains FD&C Yellow #6 (sunset yellow FCF), which may cause allergic reactions.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of cycloserine with ethionamide, isoniazid or alcohol potentiates the neurotoxicity of cycloserine. Additive neuropsychiatric effects may also be a concern when used with delamanid, and close monitoring is important, especially in children and adolescents.

Antacids do not affect absorption of cycloserine.

Food:

Intake with a high-fat meal has been shown to negatively affect the absorption of cycloserine (see section 5.2) and should be avoided.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Animal data do not indicate any teratogenicity. There are no or limited amount of data from the use of cycloserine in pregnant women.

Cycloserine should be given to pregnant women only if clearly needed and when there are no suitable alternatives.

Breastfeeding

Cycloserine passes into the breast milk.

If cycloserine is required by the mother, it is not a reason to discontinue breastfeeding. Exclusively breastfed infants should be monitored if this drug is used during lactation, possibly including measurement of serum levels to rule out toxicity if there is a concern.

For vitamin B6 substitution of the infant see section 4.4.

Fertility

There are no data on the effects of [TB330 trade name] on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of [TB330 trade name] on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of cycloserine should be borne in mind when considering the patient's ability to drive or operate machinery. Negative effects of cycloserine on the ability to drive and use machines may be synergistic with the effects of alcohol (see section 4.3).

4.8 Undesirable effects

The most frequent and most important adverse reactions of cycloserine are psychiatric and central nervous system (CNS) disorders as detailed below. CNS adverse reactions appear to be dose-related, and occur within the first 2 weeks of therapy in about 15 to 30% of patients. CNS symptoms generally disappear when the drug is discontinued.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. They are not based on adequately sized randomized controlled trials, but on published literature data generated mostly during post-approval use. Therefore, frequency data may not be available in many cases.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($\leq 1/10,000$), 'not known'.

Blood and lymphatic system disorders

Frequency not Vitamin B12 deficiency, folic acid deficiency, megaloblastic anaemia, sideroblastic anaemia

known

Cardiac disorders

Rare Cardiac arrhythmias and sudden development of congestive heart failure in patients receiving 1 g or more per day.

Hepatobiliary disorders

Not known Elevated serum transaminases, particularly in patients with liver disease

Immune system disorders

Rare Hypersensitivity reactions including rash, photosensitivity or hepatitis

Nervous system disorders

Very common headache, tremor, dysarthria, vertigo

Not known dysarthria, major and minor clonic seizures, convulsions, coma, paresis, hyperreflexia, paresthesia, peripheral neuropathy

Psychiatric disorders

Very common depression, confusion, anxiety, nervousness, drowsiness, dizziness, somnolence, lethargy

Not known disorientation, loss of memory, psychoses, suicidal tendencies, aggression, character changes,

Skin and subcutaneous tissue disorders

Not known Rash, lichenoid eruptions, Stevens-Johnson syndrome

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Acute toxicity can occur when more than 1 g is ingested by an adult. Chronic toxicity is dose related and tends to occur if more than 500 mg are administered daily. Toxicity commonly affects the central nervous system. Effects may include headache, vertigo, confusion, drowsiness, hyperirritability, paraesthesia, slurred speech and psychosis. Following ingestion of larger doses, paresis, convulsions and coma often occur.

Symptomatic and supportive therapy is recommended. Activated charcoal may be effective in reducing absorption. In adults, many neurotoxic effects can be both treated and prevented with 200 to 300 mg of pyridoxine daily. Haemodialysis removes cycloserine from the bloodstream but should be reserved for life-threatening toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of tuberculosis, Antibiotics

ATC code: J04AB01

Properties

Cycloserine is a broad-spectrum antibiotic that is bacteriostatic to *Mycobacterium tuberculosis* at the clinically recommended doses.

Mechanism of action

Cycloserine is an analog of the amino acid D-alanine. It interferes with peptidoglycan formation and bacterial cell wall synthesis.

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for [TB330 trade name]. A bioequivalence study was conducted with cycloserine 250 mg capsules which is essentially the same as [TB330 trade name] in qualitative terms and with respect to the ratio of active and other ingredients.

The absorption characteristics of [TB330 trade name] have been determined after administration of one tablet of [TB330 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value \pm standard deviation
Maximum concentration (C_{\max}) ng/mL	10.03 \pm 2.52
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng·h/mL	228.4 \pm 77.2
Time to attain maximum concentration (t_{\max}) hour	1.35 \pm 1.21

Pharmacokinetics of Cycloserine

	Cycloserine			
Absorption				
Oral bioavailability	Rapid and almost completely absorbed after oral administration			
Food effect		AUC _(0-∞)	C _{max}	T _{max}
	High fat:	No significant effect	27% ↓	2.75 h
Distribution				
Plasma protein binding <i>in vitro</i>	<20%			
Tissue distribution	Widely distributed into body tissues and fluids including lungs, ascitic fluid, pleural fluid and synovial fluid, in concentrations approximately equal to plasma concentrations of the drug			
Metabolism				
	30-40% of dose undergoes hepatic metabolism			
Active metabolite(s)	NA*- Metabolites have not yet been identified			
Elimination				
Elimination half life	Between 4 and 30 hours with mean 10 hours			
% of dose excreted in urine	60 - 70% as unchanged drug, the remainder as metabolites			
% of dose excreted in faeces	Small amounts of the drug are excreted in faeces			

*Information not available

5.3 Preclinical safety data

A study in two generations of rats given doses up to 100 mg/kg/day demonstrated no teratogenic effect in offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill: magnesium oxide
purified talc

Capsule shell: gelatin
sodium lauryl sulphate
quinoline yellow
sunset yellow (FCF/FD&C yellow#6)
titanium dioxide

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per capsule.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in the original package below 25°C.

6.5 Nature and contents of container

Blister cards

Aluminium foil on aluminium foil blister cards, each containing 10 capsules. Available in cartons of 10 x 10 capsules

Strip packs

Aluminium foil strip packs, each containing 10 capsules. Available in cartons of 10 x 10 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation and administration - extemporaneous formulation for children

Extemporaneous formulation for children

One small bowl, drinking water, a teaspoon and an oral syringe are needed for preparing the extemporaneous formulation. The following steps should be applied:

1. Open the capsule and empty its contents into the bowl then add 10 mL of drinking water and disperse by stirring gently with the spoon.
2. The required portion of the mixture (see dosing table above) should be withdrawn with the syringe. If a dose other than 10 mL is recommended, or the daily dose is to be divided, the health care provider should advise the caregiver on how to measure or divide the dose and ensure a suitable oral syringe is available for measurement.
3. The mixture should be administered immediately to the child.

4. The withdrawn mixture may be mixed with additional liquid or additional liquid may be given after administration for masking the bitter taste.

5. Any unused mixture must be discarded

7. SUPPLIER

Macleods Pharmaceuticals Limited
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Mumbai – 400 059
India

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB330

9. DATE OF PREQUALIFICATION

17 July 2018

10. DATE OF REVISION OF THE TEXT

November 2025

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<p><i>Detailed information on this medicine is available on the World Health Organization (WHO) website:</i> https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products</p>
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