Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

[TB330 trade name]†

2. Qualitative and quantitative composition

Each hard gelatin capsule contains 125 mg cycloserine.

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 capsules.

Yellow / yellow size "3" hard gelatin capsule filled with 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.

Cycloserine may be effective in the treatment of acute urinary tract infections caused by susceptible strains of Gram-positive and Gram-negative bacteria, especially Klebsiella/Enterobacter species and Escherichia coli. It is generally no more and may be 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 the more conventional therapy has failed and when the organism has been demonstrated to be sensitive to the drug

4.2 Posology and method of administration

[TB330 trade name] must always be given in combination with other antituberculosis agents. Pyridoxine (vitamin B6) should be taken concomitantly with cycloserine (see section 4.4).

Posology

Adults:

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

Children:

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. If available, therapeutic drug monitoring may be useful. Peak concentrations between 15-40 µg/mL have been recommended as appropriate.

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. 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 capsule of [TB330 trade name] in 10 mL of drinking water in order to facilitate administration, although bioavailability is uncertain. For dosing of infants weighing less than 5 kg an expert in treatment of paediatric drug-resistant tuberculosis should be consulted whenever possible.

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.

Renal failure/ dialysis:
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.

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.

Method of administration
For oral use

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Cycloserine is contra-indicated in the presence of any of the following conditions: epilepsy; depression, severe anxiety or psychosis; severe renal insufficiency; alcohol abuse

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 mcg/ml. In children, peak concentrations between 15-40 µg/mL have been recommended as appropriate. 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.

Vitamin B6 supplementation
Patients should receive pyridoxine (vitamin B6) while taking cycloserine. This is especially important while breastfeeding. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day).
Supplements should also be given to breastfed infants of mothers receiving cycloserine.

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

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 Pregnancy and Lactation

Pregnancy

Concentrations in fetal blood approach those found in the serum. 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. Cycloserine should be given to a pregnant woman only if clearly needed.

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 undesirable effects reported with Cycloserine during clinical trials and post-marketing surveillance are shown in the table below. They are listed by System-Organ Class (SOC) and in order of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Frequency of adverse events

SOC	Frequency	Event
Nervous system disorders	Not known	Convulsions, drowsiness, somnolence, headache, dysarthria, vertigo, confusion, disorientation with loss of memory, paresis, paraesthesia, localised clonic seizures, coma, dizziness
Psychiatric disorders	Not known	Psychosis, suicidal tendencies, personality change, hyper-irritability, aggression,
Musculoskeletal and connective tissue disorders	Not known	Tremor, hyper-reflexia
General disorders and administration site conditions	Not known	Hypersensitivity*
	Very rare or not known	Wheeziness, difficulty in breathing
Skin and subcutaneous disorders	Very rare	Swelling of the eyelids, face or lips, rash*, itching all over the body
Blood related disorders	Not known	Megaloblastic anaemia*
Hepatobiliary disorders	Not known	Elevated serum aminotransferases*
Cardiac disorders	Not known	Heart failure (1 to 1.5 g daily dose of Cycloserine)

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

- **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. Cycloserine is removed by haemodialysis.

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

Absorption

Cycloserine is rapidly and almost completely absorbed from the GI tract after oral administration. Following the administration of a 250 mg dose plasma levels are detectable within an hour and peak plasma concentrations of approximately 10 mg/l are achieved 3 to 4 hours after dosage administration. It is widely distributed throughout body fluids and tissues.

Distribution

There is no appreciable blood-brain barrier, and CSF levels. However, these levels are approximately the same as plasma levels. It is found in the sputum of tuberculous patients and has been detected in pleural and ascitic fluids, bile, amniotic fluid and fetal blood, breast milk, lung and lymph tissues.

Elimination

Cycloserine is excreted into the urine, levels appearing within half an hour of oral ingestion. Approximately 66 per cent of a dose appears unchanged in the urine in 24 hours. A further 10 per cent is excreted over the next 48 hours. It is not significantly excreted in the faeces.

Approximately 35 per cent is metabolised, but the metabolites have not yet been identified.

The half-life of cycloserine is in the range of 8 to 12 hours.

5.3 Preclinical safety data

There are no additional preclinical data of relevance to the prescriber beyond those already included in other sections of the Summary of Product Characteristics.

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) and Titanium dioxide

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 Content of container

Blister pack
10 capsules are packed in plain Alu/Alu cold form laminate blister cards, such 10 blister cards are packed in a carton along with the package information leaflet.
Strip pack
10 capsules are packed in plain Alu/Alu strips, such 10 strips are packed in a carton along with the package information leaflet

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.

7. Marketing Authorization Holder

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8. Marketing Authorization Number

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9. Date of first authorization/renewal of the authorization

10/12/2023

10. Date of revision of the text

12/05/2025