WHO-PQ RECOMMENDED 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

[TB416 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains Cycloserine 250mg

Excipients with potential clinical effect

Each capsule contains about 0.0174mg of FD&C yellow #6/Sunset yellow FCF

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsule

Hard gelatin capsules with an opaque red cap and an opaque grey body. The capsules are printed in black on the cap with 'S' and on the body with '455'. They contain a white to pale pink granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB416 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

[TB416 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 [TB416 trade name] may be given:

Body weight	**Daily dose**	**Number of capsules daily**
46 kg or more	750 mg	3

Children and adolescents weighing 30 kg 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 [TB416 trade name] may be given:

Body weight	**Daily dose**	**Number of capsules daily**
30 to less than 46 kg	500 mg	2

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

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 [TB416 trade name] may be given:

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

*In children weighing 7 to less than 10 kg, alternate formulations to allow for appropriate dosing, such as capsules containing 125 mg of cycloserine. If such formulations are not available, an extemporaneous preparation may be prepared by dispersing one 250 mg capsule in 10 mL of water and give 5 mL daily, although bioavailability is uncertain,

To do this, see instructions on how to prepare extemporaneous preparation in section 6.6.

Children requiring a dose of 125 mg should take 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 [TB416 trade name] in 10 mL of drinking water in order to facilitate administration, although bioavailability is uncertain. For extemporaneous preparation 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	1 mL
5 to less than 7 kg	50 mg	2 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

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

[TB416 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 [TB416 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.

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.

[TB416 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.

[TB416 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

The capsule 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 [TB416 trade name] on fertility.

4.7 Effects on ability to drive and use machines

[TB416 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

No studies on the effects of [TB416 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 (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

Blood and lymphatic system disorders

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

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

The absorption characteristics of [TB416 trade name] have been determined after administration of one Cycloserine 250mg capsule in healthy volunteers in the fasting state as follows

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	10.2 ± 2.9 µg/mL (9.8)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	177 ± 45 µg.h/mL (171)
Time to attain maximum concentration (T_{max})	0.94 ± 0.74 hours

*arithmetic mean

Pharmacokinetics of Cycloserine

<table>
<tr><td></td><td>Cycloserine</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Oral bioavailability</td><td>Rapid and almost completely absorbed after oral administration</td></tr>
<tr><td>Food effect</td><td><table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></tr><tr><td>High fat:</td><td>No significant effect</td><td>27% ↓</td><td>2.75 h</td></tr></table></td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Plasma protein binding in vitro</td><td><20%</td></tr>
<tr><td>Tissue distribution</td><td>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</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td></td><td>30-40% of dose undergoes hepatic metabolism</td></tr>
<tr><td>Active metabolite(s)</td><td>NA*- Metabolites have not yet been identified</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Elimination half life</td><td>Between 4 and 30 hours with mean 10 hours</td></tr>
<tr><td>% of dose excreted in urine</td><td>60 - 70% as unchanged drug, the remainder as metabolites</td></tr>
<tr><td>% of dose excreted in faeces</td><td>Small amounts of the drug are excreted in faeces</td></tr>
</table>

*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: Talc

Capsule shell: Gelatin
Iron oxide red
Iron oxide black
FD&C red #3/Erythrosine
Titanium dioxide
FD&C yellow #6/Sunset yellow FCF

Printing ink: Shellac
Propylene glycol
Black iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister pack

36 months

HDPE bottle pack

24 months

6.4 Special precautions for storage

Do not store above 25°C. Avoid excursions above 30°C. Protect from moisture and light.

6.5 Nature and contents of container

Blister pack

Aluminium foil blister cards, each containing 10 capsules. Available in cartons of 10 x10 capsules

HDPE bottle pack

Round, opaque white plastic (HDPE) bottle containing 40 capsules. It also contains a sachet of desiccant (drying material) and a piece of rayon wool to keep the capsules in place. The bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

Extemporaneous formulation for children

One cup, 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 cup then add 10 mL of drinking water and dissolve by stirring gently.

2. The required portion of the mixture (see dosing table above) should be withdrawn with the syringe. If a dose other than 5 or 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

Strides Pharma Science Limited
Strides House, Opp. IIMB
Bannerghatta Road
Bengaluru - 560 076,
India
Tel: +91 806784 0000
Email: corpcomm@strides.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB416

9. DATE OF PREQUALIFICATION

17 September 2025

10. DATE OF REVISION OF THE TEXT

November 2025

References

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