# 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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

# 1. NAME OF THE MEDICINAL PRODUCT

[TB154 trade name]†

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg cycloserine.

*Excipients with known effect:*

Each capsule also contains 0.2 mg carmoisine and 0.3 mg sunset yellow (FD&C YELLOW #6).

For the full list of excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Capsules.

Maroon/Maroon size '1' hard gelatin capsule filled with white to pale yellow powder.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

[TB154 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

Oral use.

[TB154 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.

| **Body weight** | **Daily dose** | **Number of capsules daily** |
|---|---|---|
| 30-45 kg | 500 mg | 2 |
| ≥46 kg | 750 mg | 3 |

***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.

Patients under 15 years of age and weighing less than 16 kg, should be given other formulations to allow appropriate dosage, e.g. capsules containing 125 mg of cycloserine.

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

If such formulations are not available, an extemporaneous preparation may be prepared by dispersing the contents of a 250-mg capsule of [TB154 trade name] in 10 mL of drinking water in order to facilitate administration in patients in lower weight-bands, 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.

Recommended daily doses are as follows:

| **Body weight of child** | **Daily dose** | **Daily volume* of extemporaneous preparation to be taken** |
|---|---|---|
| 3-4 kg | 25 mg | 1 mL |
| 5-6 kg | 50 mg | 2 mL |
| 7-9 kg | 125 mg | 5 mL |
| 10-15 kg | 250 mg | Give as 250-mg capsule** |
| ⩾16 kg | 500 mg | Give as two 250-mg capsules** |

***If a dose other than 5 or 10 mL is recommended for administration by a caregiver, 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**

**For older children weighing 16 kg or more who cannot swallow capsules, the 250-mg capsules can be opened and dispersed similarly in 10 mL water to aid administration.

For detailed instructions on preparing an extemporaneous formulation, see below: "Method of administration, extemporaneous formulation for children"

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

***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.

*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**

Cycloserine is best taken without food. It can be taken with orange juice.

## 4.3 Contraindications

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).

Concurrent use of alcohol (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 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.

[TB154 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).

**Excipients**

Each capsule of [TB154 trade name] contains the azo colouring agents carmoisine and sunset yellow (FD&C YELLOW #6), 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 [TB154 trade name] on fertility.

## 4.7 Effects on ability to drive and use machines

No studies on the effects of [TB154 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***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

### 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. 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

The absorption characteristics of [TB154 trade name] have been determined after administration of 1 capsule (containing 250 mg cycloserine) in healthy volunteers in the fasting state as follows:

| **Pharmacokinetic variable** | **Mean value* (± standard deviation)** |
|---|---|
| Maximum concentration ($C_{max}$) | 10.03 ± 2.52 ng/ml |
| Area under the curve ($AUC_{0-t}$), a measure of the extent of absorption | 159.5 ± 44.2 ng·h/ml |
| Time to attain maximum concentration ($t_{max}$) | 1.35 ± 1.21 h |

* Arithmetic mean

**Pharmacokinetics of Cycloserine**

| | **Cycloserine** |
|---|---|
| **Absorption** | |
| Oral bioavailability | Rapid and almost completely absorbed after oral administration |
| Food effect | <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>2.75hrs</td></tr></table> |
| **Distribution** | |
| Plasma protein binding *in vitro* | <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

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

Magnesium oxide

Purified talc

*Capsule shell:* Gelatin

Sodium lauryl sulfate

Methyl paraben

Propyl paraben

Brilliant blue (FD&C BLUE #1)

Carmoisine

Sunset yellow (FD&C YELLOW #6)

Titanium dioxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Alu/Alu strip pack: 24 months.

Alu/Alu cold form blister pack: 36 months.

### 6.4 Special precautions for storage

Store in the original package below 25°C.

### 6.5 Nature and contents of container

Alu/Alu foil strip of 10 capsules. Such 9 or 10 strips are packed in a carton box.

Alu/Alu cold form blister of 10 capsules. Such 9 or 10 blisters are packed in a carton box.

### 6.6 Special precautions for disposal and other handling

***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 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.

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

## 7. SUPPLIER

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## 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB154

## 9. DATE OF PREQUALIFICATION

23 March 2007

## 10. DATE OF REVISION OF THE TEXT

April 2022

***References***

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*Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines*