SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cycloserine 250 mg capsules*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg cycloserine.

Each capsule shell contains about 57 µg ponceau 4R (cochineal red A).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard Capsules.

Each hard gelatin capsule, with orange -coloured cap and white-coloured body, is filled with white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cycloserine 250 mg capsules is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

Cycloserine 250 mg capsules is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

4.2 Posology and method of administration

Oral use.

Cycloserine 250 mg capsules must always been given in combination with other antituberculosis agents.

Posology

Adults:
The usual dose is 10–15 mg/kg/day, max. 1000 mg/day given in two divided doses every 12 hours or once a day if tolerated.

Body weight	30-55.9 kg	56-70.9 kg	> 70 kg
Daily dose	500 mg	750 mg	1000 mg

Children:
10–20 mg/kg/day given 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.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Body weight	5 kg	6-9.9 kg	10-11.9 kg	12-22.9 kg	23-30 kg
Daily dose, per 250 mg capsule	0.25	0.5	0.75	1.0	2.0
1 capsule in 10 ml water	2.5 ml	5.0 ml	7.5 ml	10.0 ml*	-*

* For older children who cannot swallow capsules, the capsules can be opened and dissolved in 10 ml water to aid administration.

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

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.

To minimize 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.

Pyridoxine (vitamin B6) should be taken concomitantly with cycloserine (see section 4.4).

Method of administration
Cycloserine should best be taken without food. It can be taken with orange juice.

Duration of therapy
Therapy should be continued long enough to prevent relapse.
The duration of antituberculous 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Epilepsy.

Psychiatric disease (e.g. depression, severe anxiety, psychosis).

Concurrent use of alcohol (see 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 serially during therapy. The peak concentration should be kept below 35 mcg/ml.

Neuropsychiatric status should be assessed at baseline and 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.
Since CNS toxicity is more common with higher doses, patients receiving more than 500 mg daily should be particularly closely observed.

Patients should be monitored by hematologic, renal excretion, blood level, and liver function studies.

Cycloserine 250 mg capsules 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 these controlling symptoms.

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

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).

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

Excipients
This medicinal product contains ponceau 4R (cochineal red A), which may cause allergic reactions.

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.

Antacids do not affect absorption of cycloserine.

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

4.6 Pregnancy and lactation

Animal data do not indicate any teratogenicity. Data in human pregnancy are limited. Cycloserine should be given to pregnant women only if clearly needed and when there are no suitable alternatives.
Cycloserine passes into the breast milk. No adverse effects have been observed in breast-fed infants whose mothers were receiving cycloserine. (For Vitamin B6 substitution of the infant see section 4.4).

4.7 Effects on ability to drive and use machines

No studies on the effects 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, often no frequency data can be given.
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
Unknown: 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
Elevated serum transaminases, particularly in patients with preexisting 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.

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 more effective in reducing absorption than emesis or gastric lavage. 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 after oral administration. Following single dose administration of Cycloserine 250 mg capsules in healthy volunteers, the mean (± SD) cycloserine C_{max} value was 11.9 μg/ml (± 2.0) and the corresponding values for $AUC_{0\text{-}inf}$ was 203 μg/h/ml (± 54) and $AUC_{0\text{-}t}$ was 177 μg/h/ml (±40). The mean (± SD) cycloserine t_{max} value was 1.06 (± 0.75) hours. With repeated doses of cycloserine, there is some accumulation of the drug during the first 3 days of therapy.
Intake with a high-fat meal has been shown to delay the absorption of cycloserine and decrease $C_{max..}$

Distribution
Cycloserine is 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. Cycloserine is bound to plasma proteins to a low extent (<20%).

Elimination
The plasma half-life of cycloserine has been estimated to range between 4 and 30 hours with a mean of 10 hours. In patients with normal renal function, 60 - 70% of an oral dose of cycloserine is excreted unchanged in urine by glomerular filtration. 30-40% of the dose is metabolized in the liver. The metabolites are excreted in the urine. Small amounts of the drug are excreted in faeces.

Special populations

Renal impairment:
Since cycloserine is renally eliminated, dose adjustment is required for renal failure (see section 4.2).

5.3 Preclinical safety data

Conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction have not raised any special safety concerns for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Talc.

Capsule shell composition: Gelatin, Ponceau 4R E124 (cochineal red A), Quinoline yellow E104, Titanium dioxide E171

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25ºC, store in a dry place. Keep the bottle tightly closed to protect from moisture. Protect from light.

Discard the product 50 days after initial opening.

6.5 Nature and contents of container

HDPE bottle with HDPE screw cap, provided with a tamper-proof ring and induction foil sealing. 1 bottle with a leaflet in a carton. Pack size: 21 or 100 capsules.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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20 August 2013

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References:

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