Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Cycloserine capsules 250 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 250 mg cycloserine.For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsules.

White to creamish pink powder, filled in hard shell gelatin capsules with light orange opaque cap and white opaque body, axially imprinted with “MYLAN” over “CS250” in black ink on both the cap and body.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cycloserine capsules 250 mg 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

Cycloserine capsules 250 mg **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 dosesevery 12 hours or once a day if tolerated.

Body weight	**Daily dose**	**Number of capsulesdaily**
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. Adaily dose of 1000 mg should not be exceeded. If available, therapeutic drug monitoring may be useful. Peakconcentrations 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 allowappropriate dosage, e.g., capsules containing 125 mg of cycloserine.

If such formulations are not available, an extemporaneous preparation may be prepared by dispersing the contents of a 250-mg capsule of Cycloserine capsules 250 mg 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 tuberculosisshould be consulted whenever possible.

Recommended daily doses are as follows:

Body weight of child	**Daily dose**	**Daily volume* of extemporaneous preparation tobe 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 shouldbe 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 andgradually 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 doseis 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 oftoxicity.

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.

The extemporaneous formulation for children

One small bowl, drinking water, a teaspoon and an oral syringe are needed for preparing the extemporaneousformulation. 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 bystirring 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.

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 beparticularly closely observed.

Cycloserine capsules 250 mg 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. 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 Cycloserine capsules 250 mg on fertility.

4.7. Effects on ability to drive and use machines

No studies on the effects of Cycloserine capsules 250 mg 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 Cycloserine capsules 250 mg have been determined after administration of one cycloserine 250mg capsules in healthy human subjects under fasting state as follows

Pharmacokinetic variable	Arithmetic mean ± SD

	(geometric mean)
Maximum concentration (C_{max})	14.4 ± 5.5 (13.6) µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	242 ± 65 (234)µg.h/mL
Time to attain maximum concentration (T_{max})	0.50 (0.33 – 3.0) hours

Pharmacokinetics of Cycloserine

	Cycloserine			
Absorption				
Oral bioavailability	Rapid and almost completely absorbed after oral administration			
Food effect		$AUC_{(0-\infty)}$	C_{max}	T_{max}
	High fat:	No significant effect	27% ↓	2.75hrs
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 othersections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule fill: Talc.

Capsule shell: Gelatin, iron oxide red, iron oxide yellow and titanium dioxide Imprint ink: Shellac, propylene glycol, black iron oxide and potassium hydroxide

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Do not store above 30°C, store in tight container. Protect from moisture. Do not remove the desiccantcanister from the bottle.

Discard the product 30 days after initial opening of the bottle.

6.5. Nature and contents of container

Bottle pack

Capsules are packed in a round, wide mouth, white, HDPE bottle, fitted with a white, opaque polypropylenescrew cap and a containing a silica gel desiccant canister.
Pack size: 100 capsules.

Blister pack

The primary packs are blister cards of 10 capsules (comprised of aluminium-aluminium foil). One such blister or such 10 blisters are kept packed in a carton.
Pack size: 1 x 10 capsules and 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.

7. Marketing Authorisation holder

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8. Marketing authorization number

9. Date of first authorization/renewal of the authorisation

10. Date of revision of the text