SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cycloserine 250 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains as active ingredient 250 mg of cycloserine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Red and grey coloured hard capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Actions: Cycloserine inhibits cell wall synthesis in susceptible strains of Gram-positive and Gram-negative bacteria and in *Mycobacterium tuberculosis.*

Indications. Cycloserine is indicated in the treatment of active pulmonary and extra-pulmonary tuberculosis (including renal disease) when the organisms are susceptible to this drug and after failure of adequate treatment with the primary medications (streptomycin, isoniazid, rifampicin and ethambutol). Like all anti-tuberculous drugs, cyclosenne should be administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent.

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

Posology

Adults: The usual dosage is 500 mg to 1 g daily in divided doses, monitored by blood level determinations. The initial adult dosage most frequently given is 250 mg twice daily at 12-hour intervals for the first two weeks. A daily dosage of 1g should not be exceeded.

The elderly: As adults but reduce dosage if renal function is impaired.

Paediatric population
The usual starting dose is 10 mg/ kg/ day, then adjusted according to blood levels obtained and therapeutic response.

Method of administration

For oral administration.

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

Administration of cyclosenne should be discontinued or the dosage reduced if the patient develops allergic dermatitis or symptoms of central nervous system toxicity such as convulsions, psychosis, somnolence, depression, confusion, hyper-refiexia, headache, tremor, vertigo, paresis or dysarthria.

Toxicity is usually associated with blood levels of greater than 30mg/l, which may be the result of high dosage or inadequate renal clearance. The therapeutic index for this drug is low. The risk of convulsions is increased in chronic alcoholics (see ‘Precautions’ section).

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

Before treatment with cycloserine is begun, cultures should be taken and the susceptibility of the organism to the drug should be established. In tuberculous

infections, sensitivity to the other anti-tuberculous agents in the regimen should also be demonstrated.

Blood levels should be determined at least weekly for patients having reduced renal function, for individuals receiving a daily dosage of more than 500mg, and for those showing signs and symptoms suggestive of toxicity. The dosage should be adjusted to keep the blood level below 30mg/l.

Anticonvulsant drugs or sedatives may be effective in controlling symptoms of central nervous system toxicity, such as convulsions, anxiety or tremor. Patients receiving more than 500mg of cycloserine daily should be closely observed for such symptoms. The value of pyridoxine in preventing CNS toxicity from cycloserine has not been proven.

Administration of cycloserine and other anti-tuberculous drugs has been associated in a few instances with vitamin B_{12} and/or folic acid deficiency, megaloblastic anaemia and sideroblastic anaemia. If evidence of anaemia develops during treatment, appropriate investigations and treatment should be carried out.

Cycloserine has been associated with clinical exacerbations of porphyria and is not recommended in porphyric patients.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions: Concurrent administration of ethionamide has been reported to potentiate neurotoxic side-effects. Alcohol and cycloserine are incompatible, especially during a regimen calling for large doses of the latter. Alcohol increases the possibility and risk of epileptic episodes. Patients receiving cyclosenne and isoniazid should be monitored for signs of CNS toxicity, such as dizziness and drowsiness, as these drugs have a combined toxic action on the CNS. Dosage adjustments may be necessary.

4.6 Fertility, 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.

Breast-feeding

Concentrations in the mother's milk approach those found in the serum. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the

importance of the drug to the mother.

Fertility
It is not known whether cycloserine can affect reproductive capability.

4.7 Effects on ability to drive and use machines

Not relevant.

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)

* Especially in patients with pre-existing liver disease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continues monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

Acute toxicity can occur if more than 1 g is ingested by an adult. Chronic toxicity is dose related and can occur if more than 500 mg is administered daily. For patients with renal impairment see 'Contra-indications' and 'Warnings'. Toxicity commonly affects the central nervous system. Effects may include headache, vertigo, confusion, drowsiness, hyper-irritability, paraesthesias, dysarthria and psychosis. Following larger ingestions, paresis, convulsions and coma often occur. Ethanol may increase the risk of seizures.

Symptomatic and supportive therapy is recommended. Activated charcoal may be more effective in reducing absorption than emesis or lavage. 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: Antimycobacterials, ATC code: J04AB01

Mechanism of action
Cycloserine inhibits cell wall synthesis (by competing with D-alanine for incorporation into the cell wall) in susceptible strains of Gram-positive and Gram-negative bacteria and in *Mycobacterium tuberculosis.*

Indications: Cycloserine is indicated in the treatment of active pulmonary and extra-pulmonary tuberculosis (including renal disease) when the organisms are susceptible to this drug and after failure of adequate treatment with the primary medications (streptomycin, isoniazid, rifampicin and ethambutol). Like all anti-tuberculous drugs, cycloserine should be administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent.

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.

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

A study in two generations of rats given doses up to 100mg/ kg/ day demonstrated no teratogenic effect in offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talc
Erythrosin E127
Carmoisine E122
Sunset yellow FCF E110
Titanium Dioxide E171
Black Iron Oxide E172
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25˚C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Cycloserine capsules are red and grey.
HDPE bottles of 100 capsules fitted with a child resistant, polypropylene cap with an induction heat sealed liner. 1 desiccant disc (HDPE canister containing 3g silica gel) is included in each bottle.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Limited
8 The Chase,
John Tate Road,
Hertford,
SG13 7NN

8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: October 1996
Date of latest renewal: 31st May 2007

10 DATE OF REVISION OF THE TEXT

15/03/2023