

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terizidone Capsules 250 mg¹

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 250 mg terizidone.

Excipients with known effect

Each capsule contains 0.17 mg of sodium methyl paraben, 0.02 mg of sodium propyl paraben and 0.14 mg of carmoisine

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsules.

Blue colour cap and blue colour body size “0” hard gelatin capsule containing creamy coloured granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Terizidone Capsules 250 mg is only indicated as a second -line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

Consideration should be given to official treatment guidelines for tuberculosis, e.g. those of WHO:

<http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf>

4.2 Posology and method of administration

Oral use

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	56-70kg	≥71kg
Daily dose	500 mg	750 mg	1000 mg

¹Trade names are not prequalified by WHO. This is the national medicines regulatory agency's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Children:

10–20 mg/kg/day given in two divided doses every 12 hours. A daily dose of 1000 mg should not be exceeded.

The recommended dose for children with a body weight of 23-30 kg is 250 mg terizidone (1 capsule) twice daily. If patients cannot swallow the capsule, it can be opened and the contents dissolved in approximately 10 ml drinking water to aid administration.

For children weighing less than 23 kg an extemporaneous formulation for the administration of fractional doses has to be prepared from the 250mg capsule as follows:

The contents of one capsule should be dissolved in 10 ml drinking water and the weight-adjusted dose should then be withdrawn by use of an oral syringe with 0.25 ml markings as per the following dosing table.

Body weight	5 kg	6-9.9 kg	10-11.9 kg	12-22.9 kg
Dose (every 12 hours)	1.25 ml (31.25 mg)	2.5 ml (62.5mg)	3.75 ml (93.75 mg]	5 ml (125 mg)

The dose should be administered immediately and the remaining mixture should be discarded.

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.

Hepatic impairment:

Data on terizidone use in hepatic impairment are scarce. Patients should be carefully monitored for signs of toxicity

To minimize headaches at the start of therapy, terizidone can be started at lower doses of 250–500 mg and gradually increased over one to two weeks to achieve the target dose.

If available, therapeutic drug monitoring may be useful. Peak concentrations (approximately 2 hours after intake) should be obtained within the first 2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept below 35 µg/ml.. Patients should also be carefully monitored clinically for signs of toxicity, and doses should be adjusted accordingly.

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

Method of administration:

Terizidone 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, to cycloserine 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:

If available, therapeutic drug monitoring may be useful. Terizidone peak concentrations should be obtained within the first 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 least at monthly intervals and more frequently if neuropsychiatric symptoms develop. The most dangerous risk of terizidone 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 haematologic, renal excretion, blood level, and liver function tests

Terizidone 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.

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

Patients should receive pyridoxine (vitamin B6) while taking terizidone. This is especially important while breastfeeding. Adults need 100 mg or more (or 50 mg per 250 mg of terizidone) and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day).

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

Excipients

This medicinal product contains sodium methyl paraben, sodium propyl paraben and carmoisine, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of terizidone with ethionamide, isoniazid or alcohol potentiates the neurotoxicity of terizidone.

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

4.6 Pregnancy and Breastfeeding

Animal data do not indicate any teratogenicity. Data in human pregnancy are limited. Terizidone should be given to pregnant women only if clearly needed and when there are no suitable alternatives.

Terizidone passes into the breast milk. No adverse effects have been observed in breast-fed infants whose mothers were receiving terizidone. (For Vitamin B6 substitution of the infant see section 4.4)

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse reaction profile of terizidone should be borne in mind when considering the patient's ability to drive or operate machinery. Negative effects of terizidone 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 terizidone are psychiatric and central nervous system (CNS) disorders as detailed below. CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis and suicidal ideation, usually occur at peak concentrations $>35 \mu\text{g/ml}$, but may be seen in the normal therapeutic range. 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 ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1000, < 1/100$), rare ($\geq 1/10,000, < 1/1000$), very rare ($\leq 1/10,000$), 'not known'.

Blood and lymphatic system disorders

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

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, the active metabolite of terizidone, is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of tuberculosis, Other drugs for treatment of tuberculosis. ATC code: J04AK03

Properties

Terizidone is obtained by combining two molecules of D-cycloserine and one molecule of terephthalic di-aldehyde. It is a broad-spectrum antibiotic that is bacteriostatic to *Mycobacterium tuberculosis* at the clinically recommended doses.

Mechanism of action

Terizidone competitively blocks the enzyme that incorporates alanine into an alanyl-alanine dipeptide, interfering with peptidoglycan formation and bacterial cell wall synthesis.

5.2 Pharmacokinetic properties

Absorption

Terizidone is rapidly and almost completely absorbed after oral administration. Terizidone converts into cycloserine, likely by hydrolysis of imine groups in terizidone to cycloserine and para-phthalate, although the precise pathway of bio-transformation has not been characterised. Following single dose administration of Terizidone 250 mg capsules in healthy volunteers, the mean (\pm SD) cycloserine C_{max} value was 6.84 $\mu\text{g}/\text{ml}$ (\pm 1.42) and the corresponding values for $\text{AUC}_{0-\text{inf}}$ was 154 $\mu\text{g}\cdot\text{h}/\text{ml}$ (\pm 26) and AUC_{0-t} was 140 $\mu\text{g}\cdot\text{h}/\text{ml}$ (\pm 25). The mean (\pm SD) cycloserine t_{max} value was 1.84 (\pm 0.89) hours. Intake with a high-fat meal has been shown to delay the absorption of terizidone and decrease C_{max} .

Distribution

Terizidone 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

Elimination

The plasma half-life of terizidone has been estimated to range between 15 and 33 hours. . In patients with normal renal function, 60 - 70% of an oral dose of terizidone is excreted as unchanged cycloserine in urine by glomerular filtration. Only a small proportion of terizidone

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 terizidone 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 fill:

Microcrystalline cellulose
Disodium edetate
Hypromellose
Stearic acid

Capsule shell:

Gelatin
Sodium methyl paraben
Sodium propyl paraben
Sodium lauryl sulphate
Titanium dioxide
Brilliant blue
Carmoisine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Store in a dry place, protect from light and moisture.

6.5 Nature and contents of container

Strip packs

10 capsules are packed in a printed aluminium foil laminated with 150 gauge polyethene, such 10 strips are further packed in a carton.

Bottle packs

Round, white, HW-HDPE, 150cc, 38 – neck with continuous thread closure with pulp and HS 123 white printed liner, 38 mm with polypropylene cap. Pack size: 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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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

TB303

9. DATE OF FIRST PREQUALIFICATION/ RENEWAL OF PREQUALIFICATION

28 November 2017

10. DATE OF REVISION OF THE TEXT

April 2018

References:

1. WHO treatment guidelines for drug resistant tuberculosis. 2016 update. Available at: <http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1>
2. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, WHO 2014. Available at: http://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf;jsessionid=B0B4AFDC357AD2BDDFBA474F32198FE1?sequence=1
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5. Morton RF, et al. Studies on the absorption, diffusion, and excretion of cycloserine. Antibiot Annu 1955-56; 3: 169-72.
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8. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 2001; 108: 776-89. (PubMed id: 11533352) Correction. *ibid.*; 1029. Also available at: <http://pediatrics.aappublications.org/content/108/3/776> (accessed 20 Nov 2017).