1. NAME OF THE MEDICINAL PRODUCT

TERIZIDON, 250 mg, capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Terizidone

1 TERIZIDON capsule, hard contains 250 mg terizidone.

Excipient with known effect:
Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard

TERIZIDON is a green, opaque capsule, hard.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TERIZIDON is indicated for adults within the scope of an anti-tuberculosis combination therapy for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis* (see sections 4.4 and 5.1).
TERIZIDON may only then be used if insufficient combination partners are available due to verified resistances or incompatibilities.

The official guidelines for appropriate use of antibacterial substances must be considered.

4.2 Posology and method of administration

Posology
750-1000 mg terizidone per day are generally administered to adults in 3 or 4 single doses, meaning 3 or 4 TERIZIDON capsules, hard. The maximum daily dose is 1000 mg terizidone.

Dosage for patients with impaired renal function:
There are no recommendations for the application of terizidone for patients with renal insufficiency. Because terizidone is a *Prodrug* of the active substance cycloserine, the recommendations for cycloserine can be used as a basis:

Patients with a creatinine clearance of < 30 ml/min should be given 250 mg terizidone (equals 1 TERIZIDON capsule, hard) daily or intermittently 500 mg terizidone (equals 2 TERIZIDON capsules, hard) 3 days per week, for example Monday, Wednesday and Friday.

Please observe that terizidone can be dialyzed (peritoneal and haemodialysis). Terizidone should therefore be administered to dialysis patients immediately after dialysis. For dialysis patients who have a continuous form of dialysis, please observe the guidelines in section 4.4.

TERIZIDON is contraindicated with serum creatinine over 2 mg/dl due to severe renal insufficiency (see section 4.3).

Method of administration
The capsules, hard have to be administered equally over the course of the day unchewed with sufficient fluids (one capsule, hard every 6 or 8 hours) during mealtimes. In order to avoid compatibility disorders, the dose can be gradually increased to the optimum quantity.

Duration of application
The duration of the application of terizidone in a combination therapy with other anti-mycobacterial substances is dependent on the clinical progression, in particular on the time point of conversion and the severity of the illness, as well as the therapy regimen applied based on the resistance test. The duration of therapy generally totals 18 - 24 months after conversion has taken place.

4.3 Contraindications

- Hypersensitivity to the active substance, cycloserine or to any of the excipients listed in section 6.1
- Severe renal insufficiency (serum creatinine > 2 mg/dl)
- Severe cerebral sclerosis
- Alcoholism
- Psychological disorders (depression, severe anxiety attacks, psychoses)
- Epilepsy
- Infections with *Mycobacterium bovis* BCG

4.4 Special warnings and precautions for use

Patients should be monitored during the inpatient and outpatient therapy phases due to the possibility of psychological side effects and nervous system side effects (see section 4.8). Outpatient treatment should not be initiated unless the patient was free of side effects during the previous inpatient treatment.

There is insufficient data available on the application, dosage and evaluation of the benefit-risk ratio of terizidone in children and teenagers. The application of TERIZIDON in this age group may therefore only be carried out in exceptional situations, if insufficient other active substances are available for therapy due to a severe pathogen resistance and the risk of a progressive course of the disease is accordingly high. Therapy using TERIZIDON on children and teenagers should take place under supervision and monitoring of the effectivity and side effects. In addition, the application of TERIZIDON in this age group should only then take place if the pathogen has been confirmed susceptible to terizidone or if pathogen susceptibility can

be assumed within the scope of the case finding. A specialist experienced in the therapy of tuberculosis must be consulted.

TERIZIDON is contraindicated for patients with a case history of severe cerebral sclerosis, alcoholism, psychological disorders (depression, severe anxiety attacks, psychoses) or epilepsy because TERIZIDON can itself lead to disorders of the central nervous system (see section 4.8) and can additionally increase the risk of such side effects in the patients listed above.

Patients who take terizidone should also be given pyridoxine (vitamin B_6) to prevent neurological side effects. The recommended dose is 50 mg vitamin B_6/250 mg terizidone.

Simultaneous alcohol intake can increase the risk of disorders of the central nervous system (see section 4.8). Patients should not drink alcohol during therapy with TERIZIDON.

There are references that the simultaneous intake of terizidone and caffeine may increase the risk of side effects on the nervous system. Due to a current lack of knowledge on this subject, the simultaneous intake of caffeine in the form of food and drink should be undertaken with caution. The intake of certain beverages or stimulants with very high caffeine levels should be avoided as a precautionary measure (see section 4.5).

Terizidone, the active substance in TERIZIDON, can be dialyzed through haemodialysis and peritoneal dialysis. There are insufficient trials available which indicate that TERIZIDON is still clinically effective in case of continuous forms of dialysis (continuous peritoneal dialysis; CAPD) (see section 5.2).

Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactive influences between TERIZIDON and other medicinal substances

Index 1: Contraindicated
Index 2: Simultaneous intake not recommended
Index 3: Simultaneous intake only under monitoring of efficacy and safety

Active substance group / Active substance	Effect on simultaneous intake with TERIZIDON	Index	Clinical consequences
Antituberculotics			
Isoniazide	Increased risk of side effects on the central nervous system (dizziness, somnolence, increased risk of cramping)	**3**	Monitoring of the side effects on the central nervous system
Ethionamide	Increased risk of side effects on the central nervous system	**3**	Monitoring of the side effects on the central nervous system
Prothionamide	Increased risk of side effects on the central nervous system	**3**	Monitoring of the side effects on the central nervous system
Anticoagulants			
Cumarine	Increase in the efficacy of oral anticoagulants	**3**	Monitoring of the side effects and efficacy of the anticoagulants: if applicable dose adjustment of anticoagulants
Antiepileptic drugs			
Phenytoine	Delayed hepatic elimination of phenytoine; increased risk of intoxication with phenytoine	**3**	Monitoring of the side effects of phenytoine; if applicable dose adjustment of phenytoine
Muscle relaxants			
Suxamethonium	Extends the efficacy of succinylcholines	**3**	Monitoring of the side effects of succinycholines; if necessary dose adjustment of suxamethonium
Stimulants			
Alcohol	Increased risk of side effects on the central nervous system (cramps, epileptoid seizures). A delayed elimination of cycloserine/terizidone increased blood alcohol limits are suspected as being the cause.	**2**	Avoid simultaneous intake of alcohol (See section 4.4).
		1	TERIZIDON is contraindicated for patients with chronic alcohol consumption and alcoholism (See section 4.3).
Caffeine	The risk of side effects on the central nervous system may be increased.	**3**	See section 4.4

4.6 Fertility, pregnancy and lactation

Pregnancy

It is not known whether terizidone passes through the placenta. However, due to the fact that terizidone (prodrug) hydrolyzes to D-cycloserine, it can be expected that the intake of TERIZIDON means that relevant quantities of cycloserine do pass through the placenta and enter the embryonic blood circulation (see section 5.2).

Up to now, no or only very limited experience has been obtained with the application of cycloserine and terizidone in pregnant women. Animal experimentation studies produced no indications of direct or indirect adverse effects on health with regard to a reproduction toxicity (see section 5.3). During pregnancy, the administration of terizidone is not recommended due to side effects on the central nervous system.

Due to the lack of clinical experience, the application of TERIZIDON during pregnancy should only be carried out after careful benefit-risk assessment.

Breastfeeding
It is not known whether terizidone passes into a mother's milk. However, due to the fact that terizidone (prodrug) hydrolyzes to D-cycloserine, it can be expected that the intake of TERIZIDON leads to relevant quantities of cycloserine passing into a mother's milk (see section 5.2).

The risk of sensitisation, diarrhoea and yeast-like fungi on the mucous membranes cannot be excluded on breastfed babies.

A decision must be made on whether breastfeeding should be interrupted or treatment with TERIZIDON should be terminated. Here both the benefits of breastfeeding for the child and the benefits of the therapy for the mother should be taken into account.

Fertility
There is no data available on the effects of terizidone on fertility.

4.7 Effects on ability to drive and use machines

Due to central nervous side effects, TERIZIDON can alter reaction capabilities also when used according to the intended purpose. The ability for active participation in road traffic or the operation of machines may be restricted. This is in particular the case in interaction with alcohol.

4.8 Undesirable effects

The incidence rates of side effects are based on the following categories:

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:	frequency cannot be estimated from the available data

Nervous system disorders
Commonly, central nervous disorders such as headaches, dizziness, excitability, tremor, insomnia and a feeling of drunkenness occur.

Rarely to uncommonly, epileptoid seizures and psychological reactions of a depressive and manic kind and anxiety attacks may occur.

Gastrointestinal disorders
Rarely to uncommonly, gastrointestinal disorders in the form of nausea, abdominal pain, meteorism, digestive disorders, diarrhoea or constipation occur.

The following side effects have occurred on administration of cycloserine (terizidone is a *prodrug* of the active substance cycloserine):
Congestive cardiac insufficiency, Stevens-Johnson syndrome, rashes, megaloblastic anaemia, liver toxicity, hypersensitivity reactions, central nervous system disorders (drowsiness, somnolence, comas, headaches, tremor, dysarthria, dizziness, confusion and disorientation with memory loss, nervousness, excitability, psychoses [possibly with suicidal behaviour], paranoia, catatonia, convulsions, hyperreflexia, vision impairments, paresis, epileptoid seizures and epileptiform absence) and encephalopathy.
It can be expected that these side effects also occur on application of terizidone, as terizidone hydrolyzes into cycloserine.

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. Healthcare professionals are asked to report any suspected adverse reactions via

Bundesinstitut für Arzneimittel und Medizinprodukte
(Federal Institute for Drugs and Medical Devices)
Abt. Pharmakovigilanz
(Department of Pharmacovigilance)
Kurt-Georg-Kiesinger Allee 3
53175 Bonn
Website: www.bfarm.de

4.9 Overdose

As a result of overdose, the side effects listed in section 4.8 may worsen. The central nervous system is particularly affected. Headaches, dizziness, confusion, drowsiness, excitability, paraesthesia, dysarthria, psychoses, paresis, tremor, cramps and comas may occur.

On overdose, measures for the prevention of reabsorption and for the acceleration of elimination are required. Terizidone and cycloserine are haemodialyzable and peritoneal dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug for the treatment of tuberculosis

ATC code: J04AK03

Mechanism of action:
Terizidone is a Schiff base consisting of 2 D-cycloserine molecules and 1 molecule of terephthalaldehyde. Terizidone is hydrolyzed *in vivo* and D-cycloserine is released.

The mechanism of action of cycloserine is based on the breakdown of the bacterial cell wall synthesis through inhibition of the alanine-racemase and D-alanyl-D-alanine-synthetase. This is competitive inhibition.

TERIZIDON is a bacteriostatic chemotherapeutic agent for oral application. Terizidone is generally effective against *Mycobacterium tuberculosis*. Although several *in-vitro*- studies allow us to suspect the susceptibility of further species of bacteria against terizidone, insufficient data and experience are available on the efficacy of terizidone in the treatment of these infections. The application of terizidone should therefore be limited to the therapy of pulmonary and extrapulmonary tuberculosis, caused by *Mycobacterium tuberculosis.*

Resistance mechanism:
Based on the structural similarity (terizidone is a *prodrug* of the active substance cycloserine), it can be assumed that the resistance mechanism as described for cycloserine also applies for terizidone.

With regard to the resistance against D-cycloserine, a reduced cellular permeability and mutations in the genes encoding for D-alanine-racemase and D-alanyl-D-alanine-synthetase have been described.
A complete parallel resistance to cycloserine exists. There are no resistance commonalities between terizidone or cycloserine and other antituberculotics.

Resistance situation:
The prevalence of the obtained resistance to individual species can vary locally and over time. Therefore, local information on the resistance situation, in particular for the adequate treatment of severe infections is required.

The aim should always be to make the selection of the combination partners for the treatment of tuberculosis dependent on a susceptibility test. Terizidone should only be applied if the susceptibility of the pathogens has been verified. The same applies for the respective combination partners. If an empirical start to therapy using terizidone is absolutely necessary, a susceptibility test should be carried out parallel to the start of the treatment. If a susceptibility test is not possible (for example because of no pathogen isolation) and if, based on the local resistance situation, the efficacy of terizidone is placed in question, consultation should be held on the therapy with experts.

Generally susceptible species
Aerobic gram-positive microorganisms
Mycobacterium tuberculosis
Species with natural resistance
*Mycobacterium bovis ssp. Bacillus Calmette-Guèrin (BCG)**

* Resistance test against cycloserine

In an *in-vitro* study with *Mycobacterium-tuberculosis*- isolates from patients in Germany with variable resistance patterns (3 strains with isoniazide monoresistance, 1 strain with rifampicin monoresistance, 31 strains with isoniazide and rifampicin resistance [multi-drug resistance, of these 2 of the Beijing genotype and 5 of the Latin American genotype]), all strains tested against terizidone proved susceptible. The minimum inhibition concentration on Löwenstein-Jensen medium was < 20 µg/ml.

A study of 261 isolates in 2002 resulted in a resistance rate against cycloserine of 0.8 %.

A study with 212 *Mycobacterium-tuberculosis*-strains with multi-drug resistance from Germany (2003-May 2005) displayed a resistance rate against cycloserine of 2.4 %

In another study, 184 multi-drug resistance strains which had been isolated in Germany between 2004 and 2006 were tested for their resistance patterns. Of these isolates, 9 (= 5 %) proved resistant against cycloserine.

5.2 Pharmacokinetic properties

The Schiff base terizidone is a *prodrug*, which hydrolyses after oral intake into cycloserine.

Absorption:
Terizidone is reabsorbed quickly and almost completely from the gastrointestinal tract after oral application. In healthy test people, a maximum serum level of 1.78-6.44 µg cycloserine/ml was achieved within 0.5-5 h (median 1.5 h) after a one-off oral administration of 250 mg TERIZIDON. After repeated administration of 250 mg TERIZIDON three times per day, the maximum cycloserine concentrations fluctuated between 12.7 and 6.2 µg cycloserine/ml (average serum concentration 9 µg cycloserine/ml) during one day.
It is probable that terizidone already hydrolyzes in the gastrointestinal tract, but also in the body, and releases D-cycloserine and terephthalaldehyde. The pharmacokinetics of cycloserine are influenced to a minimal extent by orange juice and antacids, whereas very fatty foods delay adsorption. It can be expected that this also applies to terizidone.

Distribution:
Terizidone (*prodrug*) hydrolyzes to D-cycloserine. The distribution volume of cycloserine after a single administration of 500 mg terizidone lay at 112.6 L. Cycloserine is widely distributed in tissue and fluids, including cerebrospinal fluid and breast milk. Cycloserine passes through the placenta, whereby the foetal blood concentrations reach that of the mother's. The cycloserine concentrations in breast milk are stated as being 6-19 µg/ml. The concentration ratio between breast milk and plasma is 0.67–0.75. Cycloserine is not bound to serum proteins.

Biotransformation:
No specific studies have been undertaken on the metabolization of terizidone. It is probable that terizidone already hydrolyzes in the gastrointestinal tract, but also in the body, and releases D-cycloserine and terephthalaldehyde. Terephthalaldehyde has not been proven to be antibacterially effective *in vivo*. Approx. 35 % of the cycloserine is converted into as yet unspecified metabolites.

Elimination:
The elimination of terizidone is a first-order process. In healthy test people, cycloserine was eliminated after repeated administration of 250 mg TERIZIDON three times per day with a half-life period of 16 hours. Approx. 30 % of the daily terizidone dose was excreted in the form of cycloserine in the urine. The renal clearance was approx. 20 ml/min. It is known that cycloserine is mainly eliminated renally via glomerular filtration. Minor amounts of cycloserine are eliminated via the faeces.

Pharmacokinetics for special patient groups:

Elderly patients:
The excretion of terizidone takes place more slowly than in younger patients.

Patients with restricted renal function:
The half-life period of terizidone is extended.

Dialyzability:
Terizidone or cycloserine are haemodialyzable and peritoneal dialyzable. Not enough studies are available indicating that TERIZIDON remains clinically effective in case of continuous forms of dialysis (continuous peritoneal dialysis; CAPD).

5.3 Preclinical safety data

From the studies carried out on chronic toxicity, there are no indications which might lead to a suspicion of possible unknown side effects occurring in patients.

With reference to the genotoxicity, terizidone was negative in a bacterial test (Ames test) and in an *in-vitro* chromosome aberration test on human lymphocytes.
No information is available on the carcinogenic potential of terizidone.
In animal experimentation, terizidone was neither teratogenic nor embryotoxic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, gelatine, talcum, purified water, magnesium stearate (Ph. Eur.) [vegetable], copovidone, titan dioxide (E 171), iron(III) hydroxide-oxide x H_2O (E 172), indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Capsules, hard in PVC/aluminium blister packs.

Original pack containing 50 capsules, hard
Hospital pack containing 500 (10×50) capsules, hard

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

82515.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15. May 2012

10. DATE OF THE REVISION OF THE TEXT

11.2021

11. DOSIMETRY

Prescription-only medicine