PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Terbane® 250 (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Terbane 250 tablet contains 250 mg terbinafine as terbinafine hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White or almost white, round, scored, convex tablet, coded TER 250 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fungal infections of the skin caused by *Trichophyton* (e.g. *T. rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*.

TERBANE 250 is indicated in the treatment of:

- Ringworm (*Tinea corporis*, *Tinea cruris* and *Tinea pedis*) where oral therapy is considered appropriate due to the site, severity or extent of the infection.
- Onychomycosis.

4.2 Posology and method of administration

The duration of treatment varies according to the indication and the severity of the infection.

250 mg once daily.

Skin infections:

Likely durations of treatment are as follows:

Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks

Tinea corporis: 4 weeks

Tinea cruris: 2 to 4 weeks

Onychomycosis:

The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

Children:

As data is still limited, its use is not recommended.

Elderly:

There is no evidence to suggest that elderly patients require different dosages or experience side effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group.

4.3 Contraindications

- Known hypersensitivity to terbinafine hydrochloride or any of the excipients.
- Impaired liver function.

- Pregnancy and lactation, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

Liver function:

TERBANE 250 is contraindicated for patients with chronic or active hepatic disease. Before prescribing TERBANE 250, a liver function test should be performed and any pre-existing liver disease should be assessed.

Hepatotoxicity may occur in patients with and without pre-existing liver disease therefore periodic monitoring (after 4 – 6 weeks of treatment) of liver function test is recommended. TERBANE 250 should be immediately discontinued in case of elevation of liver function test.

Very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with terbinafine. In the majority of liver failure cases, the patients had serious underlying systemic conditions (see sections 4.3 and 4.8).

Patients prescribed TERBANE 250 should be instructed to report immediately any signs or symptoms suggestive of liver dysfunction such as pruritus, unexplained persistent nausea, decreased appetite, anorexia, jaundice, vomiting, fatigue, right upper abdominal pain, dark urine or pale stools. Patients with these symptoms should discontinue taking TERBANE 250 and the patient's liver function should be immediately evaluated. The therapeutic use of TERBANE 250 in patients with chronic or active liver disease has not been studied in prospective clinical trials, and therefore cannot be recommended.

Dermatological effects:

Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms) have been very rarely reported in patients taking terbinafine. If progressive skin rash occurs, TERBANE 250 treatment should be discontinued.

TERBANE 250 should be used with caution in patients with pre-existing psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

Haematological effects:

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with terbinafine. Aetiology of any blood dyscrasias that occur in patients treated with TERBANE 250 should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with TERBANE 250.

Renal function:

In patients with renal impairment (creatinine clearance less than 50 ml/min or serum creatinine of more than 300 micro mol/l) the use of TERBANE 250 has not been adequately studied, and therefore, is not recommended (see section 5.2).

Other:

TERBANE 250 should be used with caution in patients with lupus erythematosus as very rare cases of lupus erythematosus have been reported.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on TERBANE 250:

The plasma clearance of TERBANE 250 may be accelerated by medicines which induce metabolism and may be inhibited by medicines which inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of TERBANE 250 may need to be adjusted accordingly.

The following medicines may increase the effect or plasma concentration of terbinafine:
Cimetidine decreased the clearance of terbinafine by 30 %.

Fluconazole increased the C_{max} and AUC of terbinafine by 52 % and 69 % respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other medicines which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

The following medicines may decrease the effect or plasma concentration of terbinafine:

Rifampicin increased the clearance of terbinafine by 100 %.

Effect of TERBANE 250 on other medicines:

Terbinafine may increase the effect or plasma concentration of the following medicines:

Caffeine – Terbinafine decreased the clearance of caffeine administered intravenously by 21 %.

Compounds predominantly metabolised by CYP2D6 – *In vitro* and *in vivo* studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for patients receiving compounds predominantly metabolised by CYP2D6, e.g. certain members of the following medicine classes, tricyclic antidepressants (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRI's), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-I's) type B, especially if they also have a narrow therapeutic window (see section 4.4).

Terbinafine decreased the clearance of desipramine by 82 %.

In studies in healthy subjects characterised as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolisers (genotype) to poor metaboliser status (phenotype).

Information on other medicines concomitantly used with TERBANE 250 resulting in no or negligible interactions:

Studies undertaken *in vitro* and in healthy volunteers suggest that TERBANE 250 shows negligible potential to inhibit or induce the clearance of most medicines that are metabolised via other cytochrome P450 enzymes (e.g. tolbutamine, terfenadine, triazolam, oral contraceptives), with exception of those metabolised through CYP2D6 (see below).

Terbinafine does not interfere with the clearance of antipyrine or digoxin.

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further, there was no clinically relevant interaction between terbinafine and the potential co-medications co-trimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

Terbinafine may decrease the effect or plasma concentration of the following medicines:
Terbinafine increased the clearance of ciclosporin by 15 %.
Rare cases of changes in INR and/or prothrombin time have been reported in patients receiving terbinafine concomitantly with warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience with TERBANE 250 in pregnant women is very limited, TERBANE 250 should not be used during pregnancy and is contraindicated (see section 4.3).

Lactation:

Terbinafine is excreted in breast milk and therefore mothers should not receive treatment with TERBANE 250 whilst breastfeeding.

Fertility:

Foetal toxicity and fertility studies in animals suggest no adverse effects.

4.7 Effects on ability to drive and use machines

No studies on the effects of TERBANE 250 treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent: Neutropenia, thrombocytopenia and agranulocytosis

Not known: Anaemia, pancytopenia

Immune system disorders:

Less frequent: Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus

Not known: Anaphylactic reaction, serum sickness-like reaction

Metabolism and nutrition disorders:

Frequent: Decreased appetite

Psychiatric disorders:

Not known: Anxiety and depressive symptoms

Nervous system disorders:

Frequent: Headache, dysgeusia* including ageusia*

* Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the medicine. Isolated cases of prolonged hypogeusia have been reported.

Less frequent: Paraesthesia, hypoaesthesia, dizziness,

Not known: Anosmia including permanent anosmia, hyposmia

Eye disorders:

Not known: Visual impairment, vision blurred, visual acuity reduced

Ear and labyrinth disorders:

Less frequent: Vertigo

Not known: Hypoacusis, impaired hearing, tinnitus

Vascular disorders:

Not known: Vasculitis

Gastrointestinal disorders:

Frequent: Gastrointestinal symptoms (feeling of fullness abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea)

Not known: Pancreatitis

Hepatobiliary disorders:

Less frequent: Cases of serious hepatic dysfunction, including hepatic failure, hepatic enzymes increased, jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with TERBANE 250 should be discontinued (see section 4.4). Very rare cases of serious liver failure have been reported (some with a fatal outcome, or requiring liver transplant). In the majority of liver failure cases, the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine was uncertain.

Skin and subcutaneous tissue disorders:

Frequent: Rash, urticaria

Less frequent: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, toxic skin eruption, dermatitis exfoliative, dermatitis bullous, photosensitivity reactions and alopecia, psoriasiform eruptions or exacerbation of psoriasis. If progressive skin rash occurs, treatment with TERBANE 250 should be discontinued.

Not known: Serious skin reactions (e.g. acute generalised exanthematous pustulosis (AGEP)), drug rash with eosinophilia and systemic symptoms

Musculoskeletal and connective tissue disorders:

Frequent: Musculoskeletal reactions (arthralgia and myalgia)

Not known: Rhabdomyolysis

General disorders:

Less frequent: Malaise

Not known: Influenza-like illness, pyrexia, fatigue

Investigations:

Less frequent: Weight decreased**

**weight decreased secondary to dysgeusia

Not known: Blood creatine phosphokinase increased

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via

Patientsafety.sacg@novartis.com.

4.9 Overdose

A few cases of overdose (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. The recommended treatment of overdosage consists in eliminating the medicine, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.2.2 Antimicrobial (chemotherapeutic) agents. Fungicides

5.1 Pharmacodynamic properties

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations, terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity versus yeasts is fungicidal or fungistatic depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

When given orally, the medicine concentrates in the skin at levels associated with fungicidal activity.

5.2 Pharmacokinetic properties

Following oral administration, terbinafine is well absorbed (> 70 %) and the absolute bioavailability of terbinafine as a result of first-pass metabolism is approximately 50 %. A single oral dose of 250 mg terbinafine resulted in mean peak plasma concentrations of 1,30 µg/ml within 1,5 hours after administration. Plasma concentrations decline in a triphasic manner, with a terminal half-life of 16,5 days. At 28 days, when around 70 % steady state levels have been achieved, peak concentrations of terbinafine was on average 25 % higher and plasma AUC increased by a factor of 2,3 when compared to single dose administration. From the increase in plasma AUC an effective half-life of ~30 hours can be calculated. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20 %), but not sufficiently to require dose adjustments.

Terbinafine binds strongly to plasma proteins. It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum rich skins. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks of commencing therapy.

Terbinafine is metabolised rapidly and extensively by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine.

No age-dependent changes in pharmacokinetics have been observed but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of terbinafine.

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance < 50 ml/min) or with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50 %.

5.3 Preclinical safety data

In long-term studies (up to 1 year) in rats and dogs, no marked toxic effects were seen in either species up to oral doses of about 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumours was observed in males at the highest dosage level of 69 mg/kg a day.
The changes which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in the carcinogenicity study in mice, dogs or monkeys.

During high-dose studies in monkeys, refractile irregularities were observed in the retina at the higher doses (nontoxic effect level 50 mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after medicine discontinuation. They were not associated with histological changes.

A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.

No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, hypromellose, magnesium stearate, potato starch and sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Transparent or white opaque PVC form foil with white or metallic aluminium lidding foil blister packs of 14 tablets.

OR

White, round polyethylene (PE-HD) containers with white, round polyethylene tamper evident screw caps containing 14 tablets.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

A38/20.2.2/0397

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2005

10. DATE OF REVISION OF THE TEXT

18 July 2021

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Terbane 250	NS2	12/20.2.2/0094
Zambia	Terbane 250	POM	039/028

ATC Code: D01BA02 - Antifungals for systemic use

Name and address of manufacturer:

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1,
39179 Barleben,
Germany

or

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[1]Company Reg. No.: 1990/001979/07