

1.3 Product Information

1.3.1 Summary of Product Characteristics (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

Terbinafine Tablets BP 250 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated Tablet Contains:

Terbinafine Hydrochloride BP

eq. to Terbinafine 250 mg

Excipients q.s.

3. PHARMACEUTICAL FORM

Uncoated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Oral Terbinafine Tablets 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.

Oral Terbinafine Tablets is indicated in the treatment of onychomycosis.

4.2 Posology and method of administration

Adults

250mg once daily.

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

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.

Additional information on special population

Liver impairment

Terbinafine Tablets are contraindicated for patients with chronic or active hepatic disease (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Renal impairment

The use of Terbinafine Tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Elderly

There is no evidence to suggest that elderly patients (aged 65 years or above) 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 (see Precautions).

4.3 Contraindications

Known hypersensitivity to Terbinafine or to any of the excipients of Terbinafine Tablets.
Chronic or active hepatic disease.

4.4 Special warnings and precautions for use

Liver Function

Terbinafine Tablets are contraindicated for patients with chronic or active hepatic disease. Before prescribing Terbinafine Tablets, 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. Terbinafine Tablets 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 Tablets. In the majority of liver failure cases the patients had serious underlying systemic conditions (see sections 4.3 Contraindications and 4.8 Undesirable effects).

Patients prescribed Terbinafine Tablets 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 oral Terbinafine and the patient's liver function should be immediately evaluated.

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 Tablets. If progressive skin rash occurs, Terbinafine Tablets treatment should be discontinued.

Terbinafine Tablets 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, and pancytopenia) have been reported in patients treated with Terbinafine Tablets. Aetiology of any blood dyscrasias that occur in patients treated with Terbinafine Tablets should be

evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Terbinafine Tablets.

Renal function

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micromole/L) the use of Terbinafine Tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).

Other

Terbinafine Tablets 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 medicinal products and other forms of interaction

Effect of other medicinal products on Terbinafine

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

The following medicinal products 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 drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with Terbinafine.

The following medicinal products may decrease the effect or plasma concentration of Terbinafine:

Rifampicin increased the clearance of Terbinafine by 100%.

Effect of Terbinafine on other medicinal products

Terbinafine may increase the effect or plasma concentration of the following medicinal products:

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 drug classes, tricyclic antidepressants (TCA's), β -blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmic (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) 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 characterized as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), Terbinafine increased the dextromethorphan/dextrophan 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 drug concomitantly used with Terbinafine Tablets resulting in no or negligible interactions.

Studies undertaken in vitro and in healthy volunteers suggest that Terbinafine shows negligible potential to inhibit or induce the clearance of most drugs that are metabolized 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 comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking Terbinafine Tablets 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 medicinal products:

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 in pregnant women is very limited, terbinafine tablets should not be used during pregnancy unless clinical condition of the woman requires treatment with oral terbinafine and the potential benefits for the mother outweigh any potential risks for the foetus.

Lactation

Terbinafine is excreted in breast milk and therefore mothers should not receive Terbinafine Tablets treatment whilst breast-feeding.

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 Terbinafine Tablets 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

Adverse reactions are ranked under headings of frequency, using the following convention: Very common ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1,000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1,000$); Very rare ($< 1/10,000$), Not known (frequency cannot be estimated from available data).

Blood and lymphatic system disorders

Very rare: Neutropenia, agranulocytosis, thrombocytopenia

Not known: Anaemia, pancytopenia

Immune system disorders

Very rare: Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus

Not known: Anaphylactic reaction, serum sickness-like reaction

Metabolism and nutrition disorders

Very common: Decreased appetite

Psychiatric disorders

Not known: Anxiety and depressive symptoms

Nervous system disorders

Common: Headache

Uncommon: Dysgeusia* including ageusia*

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

Rare: 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

Very rare: Vertigo

Not known: Hypoacusis, impaired hearing, tinnitus

Vascular disorders

Not known: Vasculitis

Gastrointestinal disorders

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

Not known: Pancreatitis

Hepatobiliary disorders

Rare: Cases of serious hepatic dysfunction, including hepatic failure, hepatic enzymes increased, jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with Terbinafine Tablets should be discontinued (see also 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 Tablets was uncertain.

Skin and subcutaneous tissue disorders

Very common: Rash, urticaria

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, toxic skin eruption, dermatitis exfoliative, dermatitis bullous, Photosensitivity reactions, Alopecia

If progressive skin rash occurs, Terbinafine Tablets treatment should be discontinued.

Not known: Psoriasiform eruptions or exacerbation of psoriasis. Serious skin reactions (e.g. acute generalized exanthematous pustulosis (AGEP)), Drug rash with eosinophilia and systemic symptoms

Musculoskeletal and connective tissue disorders

Very common: Musculoskeletal reactions (arthralgia, myalgia).
Not known: Rhabdomyolysis

General disorders

Rare: Malaise

Not known: Fatigue, Influenza-like illness, pyrexia

Reporting of suspected adverse reactions

Reporting 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral antifungal agent (ATC code D01B A02)

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 drug concentrates in 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 from Terbinafine Tablets as a result of first-pass metabolism is approximately 50%. A single oral dose of 250mg terbinafine resulted in mean peak plasma concentrations of 1.30µg/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 clinically-relevant 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 clearance of Terbinafine Tablets 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 100mg/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 69mg/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 (non-toxic effect level 50mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after drug 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 clastogen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicone dioxide
Hydroxy propyl methyl cellulose
Purified water
Microcrystalline cellulose PH 102
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protected from light and moisture.

6.5 Nature and contents of container

Terbinafine Tablets BP 250 mg 10 tablets are packed in Alu-Pvc blister Pack. 10 such blisters are packed in carton with package insert.

6.6 Special precautions for disposal and other handling

Keep medicines out of reach of children.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

UNIZA LIFECARE PRIVATE LIMITED

SR. No. 919/7, (Old SR. No.404), Kadi-Detroj Road, Balasar,

Tal: Kadi, Dist: Mehsana, Gujarat. PIN: 382715, INDIA.

8. MARKETING AUTHORIZATION NUMBER

Will be included after marketing authorization

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION

Will be included after marketing authorization

10. DATE OF REVISION OF THE TEXT

Will be included after marketing authorization