SUMMARY OF PRODUCT CHARACTERISTICS

Terbinafine Teva 250 mg Caplets

1. Name of the medicinal product

Terbinafine Teva 250 mg Caplets

2. Qualitative and quantitative composition

Each caplet contains 281.3mg terbinafine hydrochloride, equivalent to 250mg terbinafine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Caplets for oral administration.

White to off-white, capsule shaped biconvex tablet; on one side scored and debossed "T" on each side of the score; plain on the other side of the tablet.
Terbinafine Teva 250 mg can be divided into two equal parts.

4. Clinical particulars

4.1 Therapeutic indications

- Fungal infections of the skin caused by dermatophytes such as trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum.
- Oral Terbinafine should only be used to treat extensive, severe ringworm infections (tinea corporis, tinea cruris and tinea pedis).
- Oral Terbinafine is not effective against vaginal candidiasis or pityriasis (tinea) versicolor.
- Onychomycoses (tinea unguium, ringworm of the nails) due to infection with dermatophyte organisms (hyphomycetes).

4.2 Posology and method of administration

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

Adults
250mg once daily.

Skin infections
Recommended duration of treatment:

- Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks.
- Tinea corporis, cruris: 2 to 4 weeks.
- Cutaneous candidiasis: 2 to 4 weeks.

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

Hair and scalp infections
Recommended duration of treatment:

- Tinea capitis: 4 weeks.

Tinea capitis occurs primarily in children

Onychomycosis
For most patients the duration of successful treatment is 6 to 12 weeks.
Fingernail onychomycosis: Six weeks of therapy is sufficient for fingernail infections in most cases.
Toenail onychomycosis: Twelve weeks of therapy is sufficient for toenail infections in most cases.
Some patients with poor nail outgrowth may require longer treatment. The optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for outgrowth of healthy nail.

Special population

Hepatic impairment
Terbinafine Teva 250 mg are not recommended 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 oral terbinafine 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).

Children
A review of safety experience with oral terbinafine in children, which includes 314 patients involved in the UK terbinafine Post Marketing Surveillance study, has shown that the adverse event profile in children is similar to that seen in adults. No evidence of any new, unusual or more severe reactions to those seen in the adult population have been noted. However, as data is still limited its use is not recommended.**Geriatric patients**
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. When prescribing Lamisil tablets for patients in this age group,the possibility of pre-existing impairment of liver or kidney function should be considered (see Precautions).

Method of administration
The scored caplets are taken orally with water. They should preferably be taken at the same time each day and can be taken on an empty stomach or after a meal.

Terbinafine Teva 250mg scored tablets are divisible and can be divided into two equal parts (i.e., 125 mg strength).The caplets cannot be crushed due to a bitter taste.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Chronic or active hepatic disease.

4.4 Special warnings and precautions for use

Liver Function

Terbinafine Teva 250 mg are contraindicated for patients with chronic or active hepatic disease. Before prescribing Terbinafine Teva 250 mg, 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 Teva 250 mg 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 oral terbinafine. 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 Teva 250 mg 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 oral terbinafine. If progressive skin rash occurs, Terbinafine Teva 250 mg treatment should be discontinued.

Terbinafine Teva 250 mg 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 oral terbinafine. Aetiology of any blood dyscrasias that occur in patients treated with Terbinafine Teva 250 mg should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Terbinafine Teva 250 mg.

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 oral terbinafine has not been adequately studied, and therefore, is not recommended (see section 5.2

Pharmacokinetic properties).

Other

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

Excipient

This medicine contains 1-1.5 mg, less than 1 mmol sodium (23 mg) per caplet, that is to say essentially 'sodium-free'.

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 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 Cmax 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), p-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (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/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 drug concomitantly used with terbinafine 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 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 cyclosporine by 15%.

Rare cases of changes in INR and/or prothrombin time have been reported in patients receiving terbinafine concomitantly with warfarin.

4.6 Pregnancy and lactation

Pregnancy

Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience in pregnant women is very limited, oral terbinafine 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 oral terbinafine treatment 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 oral terbinafine 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

Side effects are generally mild to moderate, and transient. The following adverse reactions have been observed in the clinical trials or during post-marketing experience.

Adverse reactions are ranked under headings of frequency, using the following convention:

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, <1/100); Rare (≥ 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 oral terbinafine 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 oral terbinafine 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, oral terbinafine 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
Investigations	
Uncommon	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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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 oral terbinafine 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 manor, 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 oral 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 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 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

Microcrystalline cellulose, sodium starch glycolate, hydroxypropyl methylcellulose, magnesium stearate, colloidal silicon dioxide.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Keep in a dark and dry place, below 25°C

6.5 Nature and contents of container

PVDC/Aluminum blister pack containing 14 caplets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. LICENCE HOLDER AND MANUFACTURER

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8. REGISTRATION NUMBER

118.69.29958

The leaflet format was revised in 11/2021 according to the Ministry of Health guidelines