For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZIMIG 250 MG

1. GENERIC NAME

Terbinafine Tablets IP 250 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Terbinafine Hydrochloride IP equivalent to Terbinafine 250 mg

3. DOSAGE FORM AND STRENGTH

Uncoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

ZIMIG tablets are 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

Route of Administration

For oral use.

Adults

250 mg 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

Hepatic impairment

ZIMIG tablets are contraindicated for patients with chronic or active liver disease (see section 4.3 *Contraindication* and 4.4 *Special Warnings and Precautions for Use*).

Renal impairment

The use of *ZIMIG* 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 5.2 *Pharmacokinetics Properties*).

Children

The adverse event profile in children is similar to that seen in adults. No evidence of any new, unusual or more severe reactions compared to those seen in the adult population has been noted. However, as data is still limited its use is not recommended.

Elderly

There is no evidence to suggest that elderly patients (aged 65 years or above) require different dosages or experience side-effects different from those of younger patients. The possibility of

impairment of liver or kidney function should be considered in this age group (see section 4.4 *Special Warnings and Precautions for Use*).

Method of administration

The tablets 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.

4.3 Contraindications

ZIMIG tablets are contraindicated in:

- Known hypersensitivity to terbinafine or to any of the excipients of the formulation.
- Chronic or active hepatic disease.

4.4. Special Warnings and Precautions for Use

Liver Function

ZIMIG tablets are contraindicated for patients with chronic or active liver disease. Before prescribing *ZIMIG* 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. *ZIMIG* 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 section 4.3 *Contraindications* and 4.8 *Undesirable Effects*).

Patients prescribed *ZIMIG* 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, *ZIMIG* tablets treatment should be discontinued.

Terbinafine 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 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 micro mol/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 *(*see section 4.3 *Undesirable Effects)*.

4.5 Drug Interactions

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 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), 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 *Special Warnings and Precautions for Use*).

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 metabolised via other cytochrome P450 enzymes (e.g. tolbutamine, terfenadine, triazolam, oral contraceptives) with exception of those metabolised through CYP2D6.

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 Use in Special Population

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 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 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

Clinical Trial and Post Marketing Data

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 including 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 *Special Warnings and Precautions for Use).* 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 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 and administration site conditions	
Rare	Malaise.
Not known	Fatigue, influenza-like illness, pyrexia.
Investigations	
Uncommon	Weight decreased** **weight decreased secondary to dysgeusia
Not known	Blood creatine phosphokinase increased.

4.9 Overdose

Symptoms and signs

A few cases of overdose of terbinafine (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 Antifungals 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 tablets as a result of first-pass metabolism is approximately 50%. A single oral dosage of 250 mg 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 dosage adjustment.

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 preexisting liver disease have shown that clearance of terbinafine may be reduced by about 50%.

6. NONCLINICAL PROPERTIES

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.

7. DESCRIPTION

Each uncoated tablet contains:

Terbinafine Hydrochloride IP equivalent to Terbinafine 250 mg

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Microcrystalline cellulose, Pregelatinised starch, Sodium starch glycollate, Magnesium stearate, Colloidal silicon dioxide, Purified water

8.1 Incompatibilities

None known.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Blister strip of tablets in a carton.

8.4 Storage and Handling Information

Store protected from light and moisture, at a temperature not exceeding 25°C.

Keep out of reach of children.

There are no special requirements for use or handling of this product

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patient's caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *ZIMIG* tablets. Patients (and/or patient's caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

22-FEB-2022

Version: ZIMTB/PI/IN/2022/01

Adapted from Lamisil Tablets 250mg – SmPC Updated on eMC on 14-Sep-2020; Date of revision of the text 04 September 2020.