1. NAME OF THE MEDICINAL PRODUCT
Terbinafine 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 250 mg terbinafine.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.
Off white, elongated, biconvex, uncoated tablets, having both sides plain.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications

Treatment of fungal infections of the skin caused by terbinafine sensitive dermatophytes in cases of *tinea corporis, tinea cruris* and *tinea pedis*, when oral therapy is considered appropriate due to the site, severity or extent of the infection.
Treatment of onychomycosis caused by terbinafine sensitive dermatophytes.
Consideration should be given to official guidance concerning the appropriate use and prescription of antifungals.
In contrast to topical terbinafine, oral terbinafine is not effective in Pityriasis versicolor

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Adults:
250 mg once daily however, the duration of treatment will vary according to the indication and the severity of the infection.

Skin Infections:
Duration of the treatment
The likely durations of treatments are as follows:
Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks
Tinea corporis: 2 to 4 weeks
Tinea cruris: 2 to 4 weeks
Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

Onychomycosis
The duration of treatment is usually between 6 weeks and 3 months. Treatment of 6 weeks for onychomycosis of the finger nails is generally sufficient. Regarding onychomycosis of the toe nails, a 12 week treatment is usually sufficient, although a few patients with poor nail outgrow may require a longer treatment duration (6 months or longer).
Complete resolution of the signs and symptoms of infection may not occur until several months after cessation of the treatment. This corresponds to the time needed for a healthy nail growth.

Children and adolescents (below 18 years of age):
There is limited experience with oral terbinafine in children and adolescents and therefore its use cannot be recommended.
Additional information on special population

Elderly:
There is no evidence to suggest that elderly patients require different dosages or experience different side effects than younger patients. When prescribing terbinafine tablets for patients in this age group, the possibility of pre-existing impairment of hepatic or kidney function should be considered (see section 4.4. Special warnings and precautions for use).

Renal impairment
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).

Liver impairment
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease (see section 4.4 Special warnings and precautions for use).

Method of administration:
The tablet should be swallowed whole with water with or without food.

4.3 Contraindications

- Hypersensitivity to terbinafine or to any of the excipients listed in section 6.1.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

Liver function
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing terbinafine tablets, liver function test should be performed. Hepatotoxicity may occur in patients with and without pre-existing hepatic disease therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended. Terbinafine should be immediately discontinued in case of elevation of liver function test. Very rare cases of serious hepatic failure (some with a fatal outcome, or requiring hepatic transplant) have been reported in patients treated with terbinafine tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine tablets was uncertain. (see section 4.8 Undesirable effects).
Patients prescribed terbinafine tablets should be warned to report immediately any signs and symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale faeces. Patients with these

symptoms should discontinue taking oral terbinafine and the patient's hepatic function should be immediately evaluated.

Dermatological effects
Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) have been very rarely reported in patients taking terbinafine tablets. If progressive skin rash occurs, terbinafine tablets treatment should be discontinued.

Haematological effects
Very rare cases of blood disorders (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with terbinafine tablets. Aetiology of any blood disorders 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).

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as there have been post-marketing reports of occurrences or deterioration of psoriasis or cutaneous/systemic lupus erythematosus.

Excipients:
Sodium
Terbinafine contains Sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, 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 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 33%.
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
According to the results from studies undertaken in vitro and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most drugs that are metabolised via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or 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 cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of irregular menstruation 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 increase the effect or plasma concentration of the following medicinal products
In studies in healthy subjects characterized as extensive metabolizers 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 metabolizer phenotype status.

Caffeine
Terbinafine decreased the clearance of caffeine administered intravenously by 19%.

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 compounds predominantly metabolised by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonine 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 4.4. Special warnings and precautions for use).
Terbinafine decreased the clearance of desipramine by 82%.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products
Terbinafine increased the clearance of ciclosporin by 15%.

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.

Breastfeeding
Terbinafine is excreted in breast milk; mothers receiving oral treatment with terbinafine should therefore not breast-feed.

Fertility
No human data on fertility are available Foetal toxicity and fertility studies in animal species 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

In general, terbinafine tablets are well tolerated. Side effects are usually mild to moderate and transient. The following adverse reactions have been observed in the clinical trials or during post marketing experience.
Adverse drug reactions from clinical trials or post-marketing experience are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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 (cannot be estimated from the available data)

Blood and lymphatic system disorders	
Very rare:	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia
Uncommon:	Anaemia.
Immune system disorders	
Very rare:	Anaphylactoid reaction, angioedema, cutaneous and systemic lupus erythematosus
Not known:	Anaphylactic reactions, serum sickness-like reaction
Metabolism and nutrition disorders	
Very common:	Decreased appetite
Psychiatric disorders	
Common:	Depression*
Uncommon:	Anxiety
Nervous system disorders	
Very Common:	Headache
Common:	Dysgeusia, Hypogeusia**including ageusia**, Dizziness
Uncommon:	Paraesthesia and hypoaesthesia
Not known:	Anosmia including permanent anosmia, Hyposmia
Eye Disorders	
Common:	Visual Impairment
Not known:	Vision blurred, visual acuity reduced
Ear and labyrinth disorders	
Uncommon:	Tinnitus
Not known:	Hypoacusis, hearing impaired
Vascular disorders	
Not known:	Vasculitis
Gastrointestinal disorders	
Very common:	Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea.
Not known:	Pancreatitis
Hepatobiliary disorders	
Rare:	Hepatic failure, hepatic enzymes increased hepatitis, jaundice, cholestasis, If hepatic dysfunction develops, treatment with terbinafine should be discontinued (see also Section 4.4).
Skin and subcutaneous tissue disorders	
Very common:	Rash, urticaria

Very rare:	Erythema multiforme ,Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP)), toxic skin eruption, .Dermatitis exfoliative, Dermatitis Bullous Psoriasiform eruptions or exacerbation of psoriasis. Alopecia,
Uncommon:	Photosensitivity reaction, photodermatosis, photosensitivity allergic reaction and polymorphic light eruption
Not known:	Drug rash with Eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia
Not known	Rhabdomyolysis
General disorders and administration site conditions	
Common:	Fatigue
Not known:	Influenza like illness, pyrexia
Investigations	
Not known:	Blood creatinine phosphokinase increased,
Uncommon:	weight decreased ***

* Anxiety and depressive symptoms secondary to dysgeusia.
** Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.
***Weight decreased secondary to hypogeusia, dysgeusia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

A few cases of overdosage (up to 5 g) 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: Dermatologicals: Antifungal for systemic use.
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.

Mechanism of action:
Terbinafine interferes specifically with fungal sterol biosynthesis at an early stage. 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.

Terbinafine does not influence the metabolism of hormones or other drugs.

When given orally, the drug concentrates in skin, nails and hair at levels associated with fungicidal activity. It is still present there 15 to 20 days after stopping treatment.
Onychomycosis.

The efficacy of terbinafine tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials (SFD301, SF5 and SF1508). Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).

In a second toenail study of dermatophytic onychomycosis, in which non-dermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.

The mean time to treatment success for onychomycosis was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing terbinafine therapy, the clinical relapse rate was approximately 15%.

Fungal infections of the skin (Tinea corporis, Tinea cruris, Tinea pedis) and yeast infections of the skin caused by the genus Candida (e.g., Candida albicans) where oral therapy is generally considered appropriate owing to the site, severity or extent of the infection.

Tinea corporis, tinea cruris
Three controlled, double blinds, randomized, multicenter studies 5OR (4-week study), 6-7OR (4-week study) and 11-21OR (6-week study), evaluated efficacy and safety of terbinafine tablets in the treatment of Tinea corporis and cruris.

Two double blinds, placebo-controlled studies (5OR, 6-7OR) evaluated the efficacy of terbinafine 125mg b.i.d.in patients diagnosed with Tinea corporis/cruris. The studies included a total of 46 patients randomized to terbinafine and 49 on placebo. There was no significant difference in terms of demographic and anamnestic data within groups. Efficacy, demonstrated by negative mycology tests and a reduction in clinical symptomatology, was evaluated at 4 weeks and at the follow-up examination. In both studies, minimal efficacy was demonstrated in patients treated with placebo compared to the efficacy of orally administered terbinafine at the end of therapy and at follow up.

The third study (11-21OR), 6 weeks, double blind, randomized, multicenter study compared efficacy and safety of terbinafine 125mg b.i.d. to griseofulvin 250mg b.i.d. One hundred twenty-six (126) patients in each group were included in the efficacy analysis. This study showed high rate of mycological cure, reduction in signs and symptoms in the terbinafine treated study arm and significantly better (93-94%) overall efficacy at the end of therapy and at follow up of terbinafine 125mg b.i.d. compared to 86-87% overall efficacy of comparator.

Tinea pedis
Two double blind, controlled studies compared terbinafine 125mg b.i.d. to placebo (39-40OR) and to griseofulvin 250mg b.i.d. (20OR) in the treatment of Tinea pedis. Both studies recruited patients with chronic, recurrent disease. In the study 39-40OR, 65% of patients on terbinafine reported mycological cure at follow up whereas none of the placebo treated patients responded. In the study 20OR, terbinafine was shown to be highly effective with 88% of cure at follow up after 6 weeks therapy compared to 45% of patients on griseofulvin. These patients when observed after 10 months reported 94% cure rate, compared to 30% efficacy of griseofulvin in the same patient population.

5.2 Pharmacokinetic properties

Absorption
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 a mean peak plasma concentration of 1.3 microgram/mL within 1.5 hours of administration. The absorption half-life is 0.8 hours. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dose adjustments.

At 28 days, when approximately 70% of steady state levels have been achieved, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3 in comparison to a single dose. From the increase in plasma AUC an effective half-life of approximately 30 hours can be calculated.

Distribution
Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. The distribution half-life is 4.6 hours. 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.

Metabolism and Excretion
Terbinafine is rapidly metabolized by 7 isoenzymes of the CYP-type, mainly by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine.

Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days.

Special populations
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.
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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 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 malesat 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 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.

An 8-week oral study in juvenile rats provided a no-toxic-effect level (NTEL) of close to 100 mg/kg/day, with the only finding being slightly increased liver weights, while in maturing dogs at ≥100 mg/kg/day (AUC values about 13x (m) and 6x (f) those in children), signs of central nervous system (CNS) disturbance including single episodes of convulsions in individual animals were observed. Similar findings have been observed at high systemic exposure upon intravenous administration of terbinafine to adult rats or monkeys.

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
Cellulose microcrystalline
Sodium starch glycolate (type A)
Silica colloidal anhydrous
Hypromellose
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
10 tablets packed in ALU/ALU blister

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder
Resonant Pharmaceuticals Pvt. Ltd
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E-Mail: www.resonantpharma.com

8. Marketing authorization number(s)
PL 16363/0322

9. Date of first authorization
25/11/2011

10. Date of revision of the text
09/10/2023

Company Contact Details
Aurobindo Pharma - Milpharm Ltd.