1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) Name of the medicinal product
TYDISIL (TERBINAFINE TABLET USP 250 MG)

1.2 Strength
Each Uncoated tablets contains:
Terbinafine Hydrochloride USP
Eq. to Terbinafine 250 mg
Excipients Q.S.

1.3 Pharmaceutical Form
Oral Uncoated Tablet

2. Qualitative and Quantitative Formula
Batch Size: 1,00,000 Tablets

Sr. No.	Ingredients	Label Claim (mg)	Actual Qty/Tablet (mg)	Actual Qty/Batch (kg)	%	Function
Dry Mixing						
1.	Terbinafine Hydrochloride USP* Eq. to Terbinafine	250.000	281.27	28.127	51.14	Antifungals
2.	Microcrystalline Cellulose BP**	-	220.73	22.073	40.132	Diluent
3.	Colloidal anhydrous silica BP		5.000	0.500	0.9090	Glidant
Binding						
4.	Hydroxy propyl methyl cellulose BP	-	25.000	2.500	4.545	Binder
5.	Isopropyl alcohol BP***	-	0.058 ml	5.800 Lit.	---	Solvent
6.	Methylene Chloride BP***		0.058 ml	5.800 Lit.	---	Vehicle
Blending & Lubrication						
7.	Magnesium stearate BP	-	3.000	0.300	0.545	Lubricant
8.	Purified Talc BP	-	5.000	0.500	0.909	Glidant
9.	Sodium starch glycolate BP	-	10.000	1.000	1.818	Disintegrant
Total weight of uncoated tablet			**550.00 mg**	**55.000 kg**	---	

*Quantity to be calculated on the basis of its potency.
**Quantity to be compensates on increasing quantity of active material.
***The materials that will not remain in the final product.

3. Pharmaceutical form

White coloured round shaped biconvex plain on both side uncoated tablets.

4. Clinical particulars:

4.1 Therapeutic Indication:

Treatment of Terbinafine tablets sensitive fungal infections such as Tinea corporis, Tinea cruris and Tinea pedis is considered appropriate due to the site, severity or extent of the infection.

The treatment of onychomycosis (Terbinafine tablets-sensitive fungal infection of the nails) caused by dermatophytes.

4.2 Posology and method of administration:

Posology

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

Liver impairment

Terbinafine tablets are contraindicated for patients with chronic or active hepatic disease

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.

Children

A review of safety experience with oral terbinafine in children, which includes 314 patients involved in the UK 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.

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.

Method of administration

The scored 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

- 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 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.

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, 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.

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 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), 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.

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 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 Adverse Drug Reactions

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 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
Investigations	
Uncommon	Weight decreased** **weight decreased secondary to dysgeusia
Not known	Blood creatine phosphokinase increased

4.7 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 tablets and the potential benefits for the mother outweigh any potential risks for the foetus.

Breast-feeding
Terbinafine tablets are excreted in breast milk; mothers receiving oral treatment with Terbinafine tablets should therefore not breast-feed.
Fertility
Foetal toxicity and fertility studies in animals suggest no adverse effects.

4.8 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.

4.9 Overdose:

Few cases of overdose (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. Recommended treatment for overdose consists of eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if required.

5. Pharmacological properties

5.1 Pharmacotherapeutic Group

Pharmacotherapeutic group: Dermatologicals; antifungals for systemic use
ATC code: D01B A02

5.2 Pharmacodynamic properties

Terbinafine tablets is an allylamine which has a broad spectrum of antifungal activity. At low concentrations Terbinafine tablets is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity versus yeasts is fungicidal or fungistatic depending on the species.
Terbinafine tablets interfere selectively with fungal sterol biosynthesis at an early stage through inhibition of the enzyme squalene epoxidase. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene in the fungal cell membrane. Both the deficiency in ergosterol and the accumulation of squalene are responsible for fungal cell death.
When given orally, the active substance concentrates in skin, hair and nails at levels associated with fungicidal activity. Measurable concentrations of the active substance are still evident 15 – 20 days after cessation of treatment.
Terbinafine tablets are used for the treatment of fungal infections of the skin and nails, which is caused by Trichophyton (e.g.T. rubrum, T.mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum. The following table outlines the range of minimum inhibitory concentrations (MIC) against the dermatophytes.

Organism	MIC rang (µg/ml)
Trichophyton rubrun	0.001 – 0.15
Trichophyton mentagrophytes	0.0001 – 0.05
Trichophyton verrucosum	0.001 – 0.006
Trichophyton violaceum	0.001 – 0.1
Microsporum canis	0.0001 – 0.1
Edidermorphyton fluccosum	0.001 – 0.05

Terbinafine tablets exhibits poor efficacy against many yeasts of the Candida species.
Terbinafine tablets in contrast to locally administered Terbinafine tablets treatment, has no effect in the treatment of Pityriasis (Tinea) versicolor.

5.3 Pharmacokinetic properties

Absorption

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 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.

Distribution

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.

Biotransformation

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.

Elimination

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%.

5.4 Preclinical safety data

The approximate LD_{50} value of Terbinafine tablets is over 4 g/kg in both mice and rats.

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 69 mg/kg, at which systemic exposure was similar to clinical exposure. The mechanism of tumour development has not been established. The clinical relevance is unknown. 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 tablets metabolite in ocular tissue and disappeared after discontinuation of the active substance. 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 undesirable effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

6. Pharmaceutical particulars

6.1 List of Excipients

Sr. No.	Excipients	Specification
1	Microcrystalline Cellulose	BP
2	Colloidal anhydrous silica	BP
3	Hydroxy propyl methyl cellulose	BP
4	Isopropyl Alcohol	BP
5	Methylene Chloride	BP
6	Magnesium Stearate	BP
7	Purified Talc	BP
8	Sodium Starch Glycolate	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Keep medicines out of reach of children.

6.5 Nature and contents of container

2 X 7 Tablets in Alu - Alu Blister.

6.6 Special precautions for disposal

No special requirements.

7. REGISTRANT

ANTILA LIFESCIENCES PVT. LTD.
Mfg. At: C-1B 305/2, 3, 4 & 5, G.I.D.C, Kerala (Bavla),
Dist. Ahmedabad, Gujarat, India.

8. DATE OF REVISION OF THE TEXT

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9. NAME AND ADDRESS OF MANUFACTURER

ANTILA LIFESCIENCES PVT. LTD.
Mfg. At: C-1B 305/2, 3, 4 & 5, G.I.D.C, Kerala (Bavla),
Dist. Ahmedabad, Gujarat, India.