1. Name of the medicinal product:

TABISAFE (Terbinafine Tablets BP 250 mg)

2. Qualitative and quantitative composition

Each Uncoated tablet contains:

Terbinafine Hydrochloride BP equivalent to Terbinafine 250 mg

S.No	Name of the Ingredient	Specification	Qty per tablet (mg)	Functional Category
	Dry mixing:			
1	Terbinafine Hydrochloride *	BP	281.250	Active
2	Microcrystalline Cellulose (PH101)**	BP	44.750	Diluent
3	Sodium Starch Glycollate (Type-A)	BP	30.000	Disintegrant
4	Colloidal Anhydrous Silica	BP	2.000	Glidant
	Binder:			
5	Hypromellose (6cps)	BP	20.000	Binder
6	Purified Water #	USP	160.000	Aqueous solvent
	Pre Lubrication			
7	Sodium Starch Glycollate (Type-A)	BP	15.000	Disintegrant
8	Colloidal Anhydrous Silica	BP	1.000	Glidant
	Lubrication			
9	Magnesium Stearate	BP	6.000	Lubricant
	Total Uncoated tablet weight:		**400.000**	

3. Pharmaceutical form

Uncoated tablet.

White, Circular, Flat tablets scrod on both sides with sides scores, Engraved “T” above and “1” below the score on one side.

4. Clinical particular

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.

4.2 Posology and method of administration

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

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.

Liver impairment

Terbinafine tablets are not recommended for patients with chronic or active hepatic disease.

Method of administration:

The tablet should be swallowed whole with water with or without food.

4.3 Contraindications

- Know hypersensitivity to terbinafine or to any of the excipients.
- 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.

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 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 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.

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

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

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

The following adverse reactions have been observed in the clinical trials or during post marketing experience.

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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 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
Not known:	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	
Not known:	Anxiety, depression*
Nervous system disorders	
Common:	Headache
Uncommon:	Hypogeusia**, ageusia**
Very rare:	Dizziness, paraesthesia and hypoaesthesia
Not known:	Anosmia
Ear and labyrinth disorders	
Not known:	Hypoacusis, hearing impaired, tinnitus
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
Not known:	hepatitis, jaundice, cholestasis
Skin and subcutaneous tissue disorders	
Very common:	Rash, urticaria
Very rare:	Erythema multiforme ,Stevens-Johnson syndrome, toxic

	epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP)). Psoriasiform eruptions or exacerbation of psoriasis. Alopecia,
Not known:	Photosensitivity reaction, photodermatosis, photosensitivity allergic reaction and polymorphic light eruption
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia
Not known	Rhabdomyolysis
General disorders and administration site conditions	
Very rare:	Fatigue
Not known:	Influenza like illness, pyrexia
Investigations	
Not known:	Blood creatinine phosphokinase increased, 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.

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.

5.2 Pharmacokinetic properties

A single oral dose of 250 mg terbinafine results in mean peak plasma concentrations of 0.97µg/ml within 2 hours after administration. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. Terbinafine binds strongly to plasma proteins (99%). 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 rapidly metabolised 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. The elimination half-life is 17 hours. There is no evidence of accumulation in the plasma.

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.

The bioavailability is about 80%, which is only slightly affected by food, and therefore a dose adjustment is not necessary.

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.

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

Tablet core: Microcrystalline Cellulose, Sodium Starch Glycolate. Colloidal Anhydrous Silica, Hypromellose, Magnesium Stearate.

6.2 Incompatibilities Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

6.5 Nature and contents of container

Clear PVDC-Alu blister pack:

3 x 10 Tablets

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

Bafna Pharmaceuticals Ltd.,

No.147, Madhavaram Redhills High Road, Grantlyon village,

Vadakarai Post,

Chennai – 600 052. India

Tel: 0091 – 44 – 26320366

8. Marketing authorisation number(s):

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9. Date of first authorisation/renewal of the authorization:

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10. Date of revision of the text

07.02.2025