

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fungafine 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine, as terbinafine hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, flat, 11 mm tablets, scored on both sides with side scores, marked “T” above and “1” below the score on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Treatment of Terbinafine sensitive fungal infections such as *Tinea corporis*, *Tinea cruris* and *Tinea pedis* (caused by Dermatophytes see Section 5.1) is considered appropriate due to the site, severity or extent of the infection.
2. The treatment of onychomycosis (terbinafine-sensitive fungal infection of the nails) caused by dermatophytes.

N.B. Orally administered terbinafine tablets are not effective against *Pityriasis versicolor*.

The official local guidelines should be borne in mind, for example, national recommendations relating to the correct use and prescription of antimicrobial drugs.

4.2 Posology and method of administration

Method of administration:

Oral use

The duration of treatment is dependent on the indication and the degree of severity of the infection.

Adults:

250mg once daily.

Skin infections

The likely durations of treatment for *Tinea pedis*, *Tinea corporis* and *Tinea cruris* are 2 – 4 weeks.

For *Tinea pedis* (interdigital, plantar/moccasin-type): recommended treatment periods may be up to 6 weeks.

Complete disappearance of the symptoms of the infection may not occur until several weeks after mycological cure.

Onychomycosis

In most patients the duration of successful treatment is 6–12 weeks.

Fingernail onychomycosis: In most cases 6 weeks' treatment is sufficient in fingernail onychomycosis.

Toenail onychomycosis: In most cases 12 weeks' treatment is sufficient in toenail onychomycosis although a few patients may require treatment up to 6 months. 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 and is only seen several months after stopping treatment, which is the time for growth of a healthy nail.

Children

A review of safety experience with oral terbinafine in children, which includes 314 patients involved in the UK LAMISIL® 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 has been noted. However, as data is still limited its use is not recommended.

Additional information on special population

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).

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).

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).

4.3 Contraindications

Known hypersensitivity to Terbinafine or to any of the excipients of Terbinafine tablets

Renal impairment

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 µmol/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 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

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 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 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)

Table 1

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

<i>Not known:</i>	erythematosis Anaphylactic reactions, serum sickness-like reaction
Metabolism and nutrition disorders	
<i>Very common:</i>	Decreased appetite
Psychiatric disorders	
<i>Not known:</i>	Anxiety, depression*
Nervous system disorders	
<i>Common:</i>	Headache
<i>Uncommon:</i>	Hypogeusia**, ageusia**
<i>Very rare:</i>	Dizziness, paraesthesia and hypoesthesia
<i>Not known:</i>	Anosmia
Ear and labyrinth disorders	
<i>Not known:</i>	Hypoacusis, hearing impaired, tinnitus
Vascular disorders	
<i>Not known:</i>	Vasculitis
Gastrointestinal disorders	
<i>Very common:</i>	Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea.
<i>Not known:</i>	Pancreatitis
Hepatobiliary disorders	
<i>Rare:</i>	Hepatic failure, hepatic enzymes increased
<i>Not known:</i>	hepatitis, jaundice, cholestasis
Skin and subcutaneous tissue disorders	
<i>Very common:</i>	Rash, urticaria
<i>Very rare:</i>	Erythema multiforme ,Stevens- Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP)). Psoriasiform eruptions or exacerbation of psoriasis. Alopecia,..
<i>Not known:</i>	Photosensitivity reaction, photodermatitis, photosensitivity allergic reaction and polymorphic light eruption
Musculoskeletal and connective tissue disorders	
<i>Very common:</i>	Arthralgia, myalgia
<i>Not known:</i>	Rhabdomyolysis
General disorders and administration site conditions	
<i>Very rare:</i>	Fatigue
<i>Not known:</i>	Influenza like illness, pyrexia
Investigations	
<i>Not known:</i>	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 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: Dermatologicals; antifungals for systemic use

ATC code: D01B A 02

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 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 is 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 range (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
Epidermorphyton fluccosum	0.001 – 0.05

Terbinafine exhibits poor efficacy against many yeasts of the Candida species.

Terbinafine tablets in contrast to locally administered terbinafine treatment, has no effect in the treatment of Pityriasis (Tinea) versicolor.

5.2 Pharmacokinetic properties

A single oral dose of 250mg terbinafine results in mean peak plasma concentrations of 0.97 mcg/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%).

Terbinafine rapidly diffuses through the skin and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and parts of the skin rich in sebaceous

glands. There is also evidence that terbinafine is distributed into the nail plate within a few weeks after commencing therapy.

Terbinafine is rapidly metabolised by the CYP-isoenzymes, 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.

In patients with pre-existing mild to severe hepatic impairment, single dose pharmacokinetic studies have shown that the clearance of Terbinafine can be reduced by 50%.

The bioavailability of terbinafine is only slightly affected by food, and therefore a dose adjustment is not necessary.

5.3 Preclinical safety data

The approximate LD₅₀ value of terbinafine 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 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

Magnesium stearate
Silica, colloidal anhydrous
Croscarmellose sodium
Hypromellose
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Blister Alu/PVC: Keep the blister in the outer carton
HDPE containers: store in the original package.

6.5 Nature and contents of container

Al/PVC-PVdC blister and HDPE tablet container with LDPE cap

Pack Sizes: 14, 28 tablets.

Not all container types or pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 436/38/1

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