LAMIRASE

Tablets

Composition
Each tablets contains Terbinafine (as hydrochloride) 250 mg.

Action
Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine hydrochloride exerts its antifungal effect by inhibiting squalene epoxidase, a key enzyme in sterol biosynthesis in fungi. This action results in a deficiency in ergosterol and a corresponding accumulation of sterol within the fungal cell. Depending on the concentration of the drug and the fungal species tested *in vitro*, Terbinafine hydrochloride may be fungicidal; however, the clinical significance of these data is unknown. *In vitro*, mammalian squalene epoxidase is only inhibited at higher (4,000 fold) concentrations.

Terbinafine has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections of the nail. *Trichophyton rubrum, Trichophyton mentagrophytes*

Blood and tissue levels of Terbinafine following oral dosing with Terbinafine hydrochloride 250 mg QD exceed *in vitro* MICs against most strains of the following organisms that can infect the nail; however, the efficacy of Terbinafine in treating nail infections due to these organisms has not been studied in controlled clinical trials.
Epidermophyton floccosum, Microsporum gypseum, Microsporum nanum,
Trichophyton verrucosum, Candida albicans, Scopulariopsis brevicaulis

Pharmacokinetics
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 manner, 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.

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

Indications
- Onychomycosis (fungal infection of the nail) caused by dermatophyte fungi.
- Tinea capitis

- Fungal infections of the skin for the treatment of 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

Contraindications

Contraindicated in individuals with hypersensitivity to Terbinafine.

Warnings

Liver Function

Terbinafine Tablets are not recommended for patients with chronic or active liver 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 and a causal association with the intake of Terbinafine Tablets was uncertain.

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. Etiology 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.

Adverse Reactions

The most frequently reported adverse events observed are listed below. In general, the adverse events were mild, transient.

Adverse Event

Headache

Gastrointestinal Symptoms
Diarrhea, Dyspepsia, Abdominal Pain, Nausea and Flatulence

Dermatologic Symptoms
Rash, Pruritus, Urticaria, Liver Enzyme Abnormalities, Taste Disturbance, and Visual Disturbance

Rare adverse events, based on worldwide experience with Terbinafine hydrochloride use include: symptomatic idiosyncratic hepatobiliary dysfunction (including cholestatic hepatitis), serious skin reactions, severe neutropenia, and allergic reactions (including anaphylaxis). Rarely, Terbinafine hydrochloride may cause taste disturbance (including taste loss) which usually recovers within several weeks after discontinuation of the drug.

Precautions

General
Changes in the ocular lens and retina have been reported following the use of Terbinafine hydrochloride in controlled trials. The clinical significance of these changes is unknown. Hepatic function (hepatic enzyme) tests are recommended in patients administered Terbinafine hydrochloride for more than six weeks.
Pre-existing liver disease or renal impairment (creatinine clearance ?50 ml/min), the use of Terbinafine hydrochloride has not been adequately studied, and therefore, is not recommended.

In patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using Terbinafine hydrochloride therapy for greater than six weeks.

Isolated cases of severe neutropenia have been reported. These were reversible upon discontinuation of Terbinafine hydrochloride with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is ?1,000 cells/mm^3, Terbinafine hydrochloride should be discontinued and supportive management started.

Pregnancy
Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers
After oral administration, Terbinafine is present in breast milk of nursing mothers. The ratio of Terbinafine in milk to plasma is 7:1. Treatment with Terbinafine hydrochloride is not recommended in nursing mothers.

Pediatric Use
The safety and efficacy of Terbinafine hydrochloride have not been established in pediatric patients.

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 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 (phenotype) status.

Information on other drug concomitantly used with Lamisil 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 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.

Dosage and Administration

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
Lamirase tablets are not recommended for patients with chronic or active liver disease.

Renal impairment
The use of Lamirase 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 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.

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 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.

Presentation
Lamirase tablets
Box of 14 tablets