

**Lamisil®**

Oral antifungal agent

**DESCRIPTION AND COMPOSITION****Pharmaceutical form**

Tablets (scored) for oral administration.

**Active substance**

Terbinafine hydrochloride

125 mg tablets (scored) for use in children: Each tablet contains 125 mg terbinafine as the hydrochloride.

250 mg tablets (scored): Each tablet contains 250 mg terbinafine as the hydrochloride.

Certain dosage strengths may not be available in all countries.

**Active moiety**

Terbinafine

**Excipients**

125 mg: magnesium stearate; hydroxypropylmethyl cellulose; microcrystalline cellulose; lactose; sodium carboxymethyl starch.

250 mg: magnesium stearate; silica colloidal anhydrous; hydroxypropylmethyl cellulose; microcrystalline cellulose; sodium carboxymethyl starch.

Pharmaceutical formulations may vary between countries.

**INDICATIONS**

Treatment of:

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

Note: In contrast to topical Lamisil, oral Lamisil is not effective in Pityriasis versicolor (also known as *Tinea versicolor*).

**DOSAGE AND ADMINISTRATION****Dosage**

The duration of treatment varies according to the indication and the severity of the infection.

## **Adults**

250 mg once daily.

## **Skin infections**

Recommended duration of treatment:

- Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks.
- Tinea corporis, T. cruris: 2 to 4 weeks.
- Cutaneous candidiasis: 2 to 4 weeks.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

## **Hair and scalp infections**

Recommended duration of treatment:

- Tinea capitis: 4 weeks.

Tinea capitis occurs primarily in children.

## **Onychomycosis**

For most patients the duration of successful treatment is 6 to 12 weeks.

### **Fingernail onychomycosis**

Six weeks of therapy is sufficient for fingernail infections in most cases.

### **Toenail onychomycosis**

Twelve weeks of therapy is sufficient for toenail infections in most cases.

Some patients with poor nail outgrowth may require longer treatment. The optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for outgrowth of healthy nail.

## **Special populations**

### **Hepatic impairment**

Lamisil tablets are contraindicated for patients with chronic or active hepatic disease (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

## Renal impairment

The use of Lamisil tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section WARNINGS AND PRECAUTIONS and section PHARMACOKINETICS (PK)).

## Geriatric Patients

There is no evidence to suggest that elderly patients (aged 65 years and above) require different dosages or experience different side effects than younger patients. When prescribing Lamisil tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see section WARNINGS AND PRECAUTIONS).

## Pediatric Patients

No data are available in children under two years of age (usually <12 kg).

Children weighing <20 kg 62.5 mg (half a 125 mg tablet) once daily

Children weighing 20 to 40 kg 125 mg (one 125 mg tablet) once daily

Children weighing >40 kg 250 mg (two 125 mg tablets) once daily

## 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.

## CONTRAINDICATIONS

- Known hypersensitivity to terbinafine or to any of the excipients of Lamisil tablets.
- Chronic or active hepatic diseases

## WARNINGS AND PRECAUTIONS

### Liver function

Lamisil tablets are contraindicated for patients with chronic or active hepatic disease. Before prescribing Lamisil tablets, liver function tests should be performed. Since hepatotoxicity may occur in patients with and without pre-existing liver disease. Therefore periodic monitoring (after 4-6 weeks of treatment) of liver function tests is recommended. Lamisil should be immediately discontinued in case of elevation of liver function tests. Very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with Lamisil tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions (see sections CONTRAINDICATIONS AND ADVERSE DRUG REACTIONS). Patients prescribed Lamisil tablets should be warned to report immediately any symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or

jaundice, dark urine or pale feces. 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, drug rash with eosinophilia and systemic symptoms) have been very rarely reported in patients taking Lamisil tablets. If progressive skin rash occurs, treatment with Lamisil tablets should be discontinued.

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as precipitation and exacerbation of psoriasis and cutaneous and systemic lupus erythematosus have been reported in a post-marketing setting.

### **Haematological effects**

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with Lamisil tablets. Etiology of any blood dyscrasias that occur in patients treated with Lamisil tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Lamisil 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 Lamisil tablets has not been adequately studied, and therefore, is not recommended (see section PHARMACOKINETICS (PK)).

### **Interactions**

*In vitro* and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolized 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, should be followed up, especially if the co-administered drug has a narrow therapeutic window (see section INTERACTIONS).

### **Other**

Lamisil 125 mg tablets contain lactose (21 mg/tablet). Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Lamisil 125 mg tablets.

## **INTERACTIONS**

### **Observed interactions to be considered**

## **Interactions affecting the use of Lamisil**

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 Lamisil 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%.

## **Interactions resulting in effects on other medicinal products**

### **Terbinafine may increase the effect or plasma concentration of the following medicinal products**

#### **Compounds predominantly metabolized 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 metabolized 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 section WARNINGS AND PRECAUTIONS).

Terbinafine decreased the clearance of desipramine by 82% (see section WARNINGS AND PRECAUTIONS).

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 metabolizers (genotype) to poor metabolizer phenotype status.

#### **Caffeine**

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

### **Information on other drugs concomitantly used with Lamisil resulting in no or negligible interactions**

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 metabolized via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolized through CYP2D6 (see above).

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 irregularities have been reported in patients taking Lamisil 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%.

### **Drug-food/ drink interactions**

The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dose adjustments.

## **WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY**

### **Women of child-bearing potential**

Some cases of menstrual irregularities have been reported in patients taking Lamisil tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

There are no data to support special recommendations for women of child-bearing potential.

### **Pregnancy**

Foetal toxicity studies with terbinafine in animals suggest no adverse effects. Since documented clinical experience in pregnant women is very limited, Lamisil tablets should not be used during pregnancy unless the potential benefits outweigh any potential risks.

### **Breast-feeding**

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

### **Fertility**

There is no relevant information from human experience. Fertility studies in rats indicated no adverse findings in fertility or reproductive performance.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Lamisil 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.

## ADVERSE DRUG REACTIONS

Adverse drug reactions from clinical trials or post-marketing experience (Table 1) 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 group, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ )

**Table 1 Adverse drug reactions from clinical trials and post-marketing experience**

<b>Blood and lymphatic system disorders</b>	
Uncommon	Anemia
Very rare	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia.
<b>Immune system disorders</b>	
Very rare	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.
<b>Psychiatric disorders</b>	
Common	Depression
Uncommon	Anxiety
<b>Nervous system disorders</b>	
Very common	Headache
Common	Dysgeusia* including ageusia*, dizziness
Uncommon	Paresthesia and hypoesthesia
<b>Eye disorders</b>	
Common	Visual impairment
<b>Ear and labyrinth disorders</b>	
Uncommon	Tinnitus
<b>Gastrointestinal disorders</b>	
Very common	Gastrointestinal symptoms (abdominal distension, decreased appetite, dyspepsia, nausea, mild abdominal pain, diarrhea).
<b>Hepatobiliary disorders</b>	
Rare	Hepatic failure, hepatitis, jaundice, cholestasis, hepatic enzyme increased (see section WARNINGS AND PRECAUTIONS)
<b>Skin and subcutaneous tissue disorders</b>	
Very common	Rash, urticaria.

Uncommon	Photosensitivity reaction
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis), erythema multiforme, toxic skin eruption, dermatitis exfoliative, dermatitis bullous. Psoriasiform eruptions or exacerbation of psoriasis. Alopecia
<b>Musculoskeletal and connective tissue disorders</b>	
Very common	Musculoskeletal reactions (arthralgia, myalgia).
<b>General disorders and administration site conditions</b>	
Uncommon	Pyrexia
Common	Fatigue.
<b>Investigations</b>	
Uncommon	Weight decreased**

\*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 dysgeusia.

### Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Lamisil via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)**

**Immune system disorders**

Anaphylactic reaction, serum sickness-like reaction.

**Nervous system disorders**

Anosmia including permanent anosmia, hyposmia.

**Eye disorders**

Vision blurred, visual acuity reduced.

**Ear and labyrinth disorders**

Hypoacusis, impaired hearing

**Vascular disorders**

Vasculitis.

**Gastrointestinal disorders**

Pancreatitis.

**Skin and subcutaneous tissue disorders**

Drug rash with eosinophilia and systemic symptoms.

**Musculoskeletal and connective tissue disorders**

Rhabdomyolysis.

**General disorders and administration site conditions**

Influenza-like illness.

### **Investigations**

Blood creatine phosphokinase increased.

## **OVERDOSAGE**

A few cases of overdosage (up to 5 g) have been reported, giving rise to headache, nausea, epigastric 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.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of action (MOA)**

Terbinafine is an allylamine which has a broad spectrum of activity against fungal pathogens of the skin, hair and nails including dermatophytes such as Trichophyton (e.g. *T. rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. tonsurans*, *T. violaceum*), Microsporium (e.g. *M. canis*), Epidermophyton floccosum, and yeasts of the genera *Candida* (e.g. *C. albicans*) and *Malassezia*. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. Its activity against yeasts is fungicidal or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. 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.

### **Pharmacodynamic (PD)**

When given orally, terbinafine accumulates in skin, hair and nails at levels associated with fungicidal activity.

## **PHARMACOKINETICS (PK)**

### **Absorption**

Following oral administration, terbinafine is well absorbed (>70%). 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. At steady-state (70% steady state is achieved in approximately 28 days), in comparison to a single dose, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3.

### **Distribution**

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and accumulates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks after commencing therapy.

### **Biotransformation/ Metabolism**

Terbinafine is metabolized 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.

### **Elimination**

The metabolites are excreted predominantly in the urine. From the increase in plasma AUC at steady state an effective half-life of ~ 30 hours was calculated. Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days.

### **Bioavailability**

The absolute bioavailability of terbinafine from Lamisil tablets as a result of first-pass metabolism is approximately 50%.

### **Special populations**

No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been observed.

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50 mL/min) or with pre-existing liver disease have shown that the clearance of Lamisil tablets may be reduced by about 50%.

## **CLINICAL STUDIES**

### **Onychomycosis**

The efficacy of Lamisil 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 Lamisil therapy, the clinical relapse rate was approximately 15%.

### **Tinea capitis**

In the three comparative efficacy studies SF 8001, SFE 304, SF 8002 oral Lamisil (62.5 – 250 mg daily) was given to a total of 117 evaluable patients, of whom over 95% were children. Single daily doses were given after the evening meal for 4 weeks (Lamisil) or 8 weeks (griseofulvin). Efficacy, demonstrated by negative mycology tests and a reduction in symptomatology, was evaluated at 8 weeks and at the follow-up examination (Week 12 for Studies SF 8001 and SFE 304, Week 24 for Study SF 8002). Negative mycology test results at follow-up were achieved by 93%, 88% and 72% of patients given Lamisil in the three studies – the corresponding figures for griseofulvin were 88%, 89% and 69%. The derived variable “effective treatment” (negative mycology plus no, or only mild, symptoms and signs) was achieved in 82%, 78% and 69% of Lamisil-treated patients, compared with 66%, 74% and 59% in patients given griseofulvin; the difference was statistically significant in favor of Lamisil in Study SF 8001.

A 12-week randomized, double-blind, parallel group study was conducted in the United States and in Canada in children with Tinea capitis infection due to Trichophyton species (SFO327C T201). The objective of the study was to determine the optimal duration (1, 2 or 4 weeks) and safety of treatment with Lamisil (tablets), given at weight adjusted doses once daily. The primary efficacy criterion, Complete Cure at end of study, increased as Lamisil treatment duration increased (1 week, 42%, 2 weeks, 49.1% and 4 weeks, 55.6) however, differences between treatment groups were not significant. Lamisil 1-week treatment group showed the least efficacy throughout the study for all efficacy variables.

### **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**

One multicenter, double blind, randomized placebo controlled study (6-7OR) evaluated the efficacy and safety of Lamisil tablets in the treatment of Tinea corporis and cruris and two double blind randomized studies (5OR and 11-21OR(multicenter)), evaluated the efficacy and safety of Lamisil tablets in the treatment of Tinea corporis.

Two double blind, placebo controlled studies (5OR, 6-7OR) evaluated the efficacy of Lamisil 125mg b.i.d. in patients diagnosed with Tinea corporis/cruris. The studies included a total of 46 patients randomised to Lamisil 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 Lamisil at the end of therapy and at follow up.

The third study (11-21OR), a 6 weeks, double blind, randomised, multicenter study compared efficacy and safety of Lamisil 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.

Effective therapy (microscopy and culture negative and no or minimal signs and symptoms) for Lamisil Vs Griseofulvin were 93% Vs 87% at end of therapy and 94% Vs 86% at follow-up.

In a double blind, placebo controlled 4 weeks study SF 00438, Lamisil 125 b.i.d was compared to placebo in patients with cutaneous candidiasis. Twenty two patients were randomised to each treatment arm, of which 19 were evaluated respectively. At week 4 follow-up, a significantly greater proportion of patients in the Lamisil group were "Effectively" treated (negative mycology and minimal or no signs and symptoms) (p = 0.029). In the Lamisil group, 9/19 (47%) patients were "Effectively" treated compared to 2/19 (11%) in the placebo group. 29% of patients in the treatment arm and 17% of patients on placebo demonstrated negative mycology at the end of treatment and 67% of Lamisil treated patients had negative mycological results at the end of follow up compared to 47% for placebo.

Two double blind, controlled studies compared Lamisil 125mg b.i.d. to placebo (39-40OR) and to griseofulvin 250mg b.i.d. (20OR) in the treatment of Tinea pedis. In the study 39-40OR, 65% of patients on Lamisil reported effective treatment (negative mycology and minimal or no signs and symptoms) at follow up whereas none of the placebo treated patients responded. In the study 20OR, Lamisil was shown to be effective in 88% of patients at follow up after 6 weeks therapy compared to 45% of patients on griseofulvin..

**Table 3 Major efficacy studies – Tinea corporis/cruris, Tinea pedis, Candida infections**

Study	Type	Drug	No. of evaluable patients	Dropouts	Mycological results % negative		Clinical results	
					End Rx	F/up	End Rx	F/up
5OR	4wk DB-placebo	Lamisil 125 b.i.d	13	4	64	89	54	62
		Placebo	15	2	0	0	0	0
6-7OR	4wk DB-placebo	Lamisil 125 b.i.d	33	8	97	97	85	91
		Placebo	34	6	29	36	12	12
11-21OR	6wk 125 b.i.d. DB-Griseofulvin	Lamisil 125 b.i.d	126	13	95	100	93	94
		Griseofulvin 250 b.i.d	126	16	88	94	87	86
SF 00438	2wk DB-placebo	Lamisil 125 b.i.d	19	3	29	67	11	47
		Placebo	19	3	17	47	11	11
39-40OR	6wk 125 b.i.d. DB-placebo	Lamisil 125 b.i.d	23	3	68	77	59	65
		Placebo	18	6	13	0	0	0
20OR	6wk 125 b.i.d. DB-Griseofulvin	Lamisil 125 b.i.d	16	2	94	100	75	88
		Griseofulvin 250 b.i.d	12	6	27	55	27	45

## NON-CLINICAL 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 tumors was observed in males at the highest dose 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 the carcinogenicity study in mice or in other studies 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 50 mg/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  $\geq 100$  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.

## INCOMPATIBILITIES

None known.

## STORAGE

See folding box.

Lamisil tablets should not be used after the date marked "EXP" on the pack.

## INSTRUCTIONS FOR USE AND HANDLING

Lamisil tablets must be kept out of the reach and sight of children.

### Manufacturer:

See folding box.

## **International Package Leaflet**

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**Novartis Pharma AG, Basel, Switzerland**