Summary Product Characteristics for Pharmaceutical Product

1. NAME OF THE MEDICINAL PRODUCT

Lamisil 125 mg tablets
Lamisil 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lamisil 125 mg tablets
Each tablet contains 125 mg terbinafine as the hydrochloride.

Excipient with known effect
Each tablet contains 21 mg lactose.

Lamisil 250 mg tablets
Each tablet contains 250 mg terbinafine as the hydrochloride.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablets (scored).

Lamisil 125 mg tablets
Whitish to yellow-tinged white, circular, biconvex, bevelled edge, approx. 9 mm tablet, smooth or slightly rough, scored and coded LP on one side.

Lamisil 250 mg tablets
Whitish to yellow tinged white, circular biconvex, with bevelled edges tablet, scored on one side and coded LAMISIL 250 (circular) on the other, diameter approx. 11 mm, smooth or slightly rough surface.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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).

4.2 Posology and method of administration

Posology
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

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 sections 6 Warnings and precautions and Pharmacokinetics (PK)).

Hepatic impairment
Lamisil tablets are contraindicated for patients with chronic or active hepatic disease (see sections 5 Contraindications and 6 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

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 6 Warnings and precautions).

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
- Known hypersensitivity to terbinafine 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
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 Contraindications and 7 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 5.2).

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 4.5).

Drug Resistance
Drug resistance has been reported with the use of Lamisil in dermatophytes, especially *Trichophyton* species (see section 5.1). Prescribers should take into consideration the local prevalence of drug resistance and if an alternate treatment should be considered.

Excipients
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of 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 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%.

Interactions resulting in effects on other medicinal products
Terbinafine may increase the effect or plasma concentration of the following medicinal products 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 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 4.4).

Terbinafine decreased the clearance of desipramine by 82% (see section 4.4).

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 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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate or well-controlled clinical trials using terbinafine in pregnant women. In an observational, registry-based cohort study, there was no increase in the risk of major malformations or spontaneous abortion in pregnancies exposed to oral terbinafine in comparison to those not exposed to oral terbinafine (see Human Data).

In animal reproduction studies, terbinafine did not cause reproductive toxicity in rats and rabbits at oral doses up to 12 and 23 times the maximum recommended human dose (MRHD) based on body surface (BSA), respectively (see Animal Data).

The use of terbinafine may be considered during pregnancy, if necessary.

A nationwide, observational, registry-based cohort study was conducted in Denmark from January 1, 1997 to December 31, 2016 in a cohort of 1,650,649 pregnancies. Pregnancies were matched on propensity scores comparing pregnancies exposed to oral terbinafine versus those not exposed to oral terbinafine in a 1:10 ratio to evaluate the risk of major malformations (522 versus 5220) and spontaneous abortions (891 versus 8910).

The prevalence odds ratio for the risk of major malformations was 1.01 (95% CI, 0.63-1.62) for pregnancies exposed versus not exposed to oral terbinafine. The hazard ratio for the risk of spontaneous abortion was
1.06 (95% CI, 0.86-1.32) for the same comparison. No increased risk of major malformations or spontaneous abortion was identified among pregnancies exposed to oral terbinafine.

Animal data
In embryo-fetal development studies in rats and rabbits, terbinafine was administered orally (30, 100, or 300 mg/kg/day) during the period of organogenesis. There were no embryotoxic or teratogenic effects up to the maximum tested dose of 300 mg/kg/day in rats and rabbits (corresponding to 12 and 23 times the MRHD based on BSA, respectively). Subcutaneous administration of terbinafine (10, 30 or 100 mg/kg/day) to rats during the period of organogenesis showed no teratogenic or embryotoxic effect up at doses up to 100 mg/kg/day (corresponding to 4 times the MRHD based on BSA).

In a rat peri-and postnatal development study, oral administration of terbinafine (30, 100 or 300 mg/kg/day) had no adverse effects on pregnancy and lactation at doses up to 300 mg/kg/day (corresponding to 12 times the MRHD based on BSA). No treatment related effects in F1 and F2 generations were noted.

Lactation
Terbinafine is transferred into human breast milk. There are no data on the effects of terbinafine on the breastfed child or on milk production. The maximum ratio of terbinafine in milk to plasma is 7:1, and the maximum amount of terbinafine ingested by the infant is expected to be 16% of the dose administered to the nursing mother. The highest concentration of terbinafine in breast milk was observed within 6 hours after administration, and thereafter the concentration of terbinafine decreased by approximately 70% in the 6-12 hour time window after administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lamisil and any potential adverse effects on the breast-fed child from Lamisil.

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

Infertility
There is no relevant information from human experience. Fertility studies in rats indicated no adverse findings in fertility or reproductive performance (see section 5.3).

4.7 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.

4.8 Undesirable effects

Adverse drug reactions from clinical trials or post-marketing experience 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 grouping, 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions from clinical trials and post-marketing experience

Blood and lymphatic system disorders	
Uncommon:	Anemia.
Very rare:	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia.
Immune system disorders	
Very rare:	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.
Psychiatric disorders	
Common:	Depression.
Uncommon:	Anxiety.
Nervous system disorders	
Very common:	Headache.
Common:	Dysgeusia* including ageusia*, dizziness.
Uncommon:	Paresthesia and hypoesthesia.
Eye disorders	
Common:	Visual impairment.
Ear and labyrinth disorders	
Uncommon:	Tinnitus.
Gastrointestinal disorders	
Very common:	Gastrointestinal symptoms (abdominal distension, decreased appetite, dyspepsia, nausea, mild abdominal pain, diarrhea).
Hepatobiliary disorders	
Rare:	Hepatic failure, hepatitis, jaundice, cholestasis, hepatic enzyme increased (see section 6 Warnings and precautions)
Skin and subcutaneous tissue disorders	
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.
Musculoskeletal and connective tissue disorders	
Very common:	Musculoskeletal reactions (arthralgia, myalgia).
General disorders and administration site conditions	
Uncommon:	Pyrexia.
Common:	Fatigue.
Investigations	
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 7-2 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, hearing impaired
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral antifungal agent (ATC code D01B A02).

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

Drug resistance

The potential terbinafine resistance in dermatophytes may be associated with mutations in erg1, the target gene for squalene epoxidase/monooxygenase (SQLE). There have been reports of some *Trichophyton* isolates (such as *T. mentagrophytes, T. indotinae, T. rubrum, T. interdigitale*) with reduced susceptibility to terbinafine, suggesting a potential for development of drug resistance (see section 4.4). The clinical significance of this observation is not fully understood.

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*), Microsporum (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.

Clinical efficacy and safety

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 97% 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 85%, 88% and 72% of patients given Lamisil in the three studies – the corresponding figures for griseofulvin were 73%, 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.

Two phase II treatment duration finding studies totaling 342 patients (mostly children) with T. capitis have been completed.

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.

A second 16-week randomized, active-controlled, parallel-group, multicenter study was conducted in Europe in patients with *Tinea capitis* (>4 years) due to Microsporum species. The Lamisil treatment duration arms (6,8,10, and 12 weeks) were double blinded, while the Griseofulvin active comparator arm was open-label (SFO327C T202). The objective of the study was to identify a safe and most appropriate treatment duration with Lamisil (tablets) in patients with *Tinea capitis* caused by Microsporum species. Dose administration of Lamisil was based on body weight in both studies as follows: <20 kg: 62.5 mg, 20-40 kg: 125 mg, >40 kg: 250 mg, given once daily. In both studies, Lamisil was very well tolerated. Analysis of the efficacy data showed that both 2 and 4-week treatment duration provided good efficacy in T. capitis caused by Trichophyton species. In the Microsporum study, there was no significant difference in complete cure rates between the different treatment duration groups and 6-week treatment showed high complete cure rate (62%) with good tolerability and compliance. These results show that Lamisil reduced treatment duration from 6-8 weeks to only 2-4 weeks in T. capitis caused by Trichophyton species compared to standard therapy with griseofulvin.

In phase II clinical studies conducted in *Tinea capitis*, adverse events reported from the 588 children enrolled were, in general, mild, relatively infrequent and often had an uncertain relationship to treatment. There were 11 reports of elevated SGPT levels and one of taste loss. Other events included mild gastrointestinal or skin symptoms, and laboratory findings indicative of intercurrent infections.
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.

Three controlled, double blind, randomised, multicenter studies 5OR (4 week study), 6-7OR (4 week study) and 11-21OR (6 week study), evaluated efficacy and safety of Lamisil tablets in the treatment of Tinea corporis and cruris.

Two double blind, placebo controlled studies (5OR, 6-7OR) evaluated the efficacy of Lamisil 125 mg 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 125 mg b.i.d. to griseofulvin 250 mg b.i.d. One hundred twenty-six (126) patients in each group were included in the efficacy analysis. This study showed high rate of mycological cure, reduction in signs and symptoms in the Lamisil treated study arm and significantly better (93-94%) overall efficacy at the end of therapy and at follow up of Lamisil 125 mg

b.i.d. compared to 86-87% overall efficacy of comparator.

In summary, Lamisil 125 mg b.i.d. administered for the period of 4-6 weeks demonstrated statistically superior efficacy compared to placebo and marketed drug griseofulvin in the treatment of *Tinea corporis/cruris* in the above major efficacy studies.

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. Of those, 29% of patients in the treatment arm and 17% of patients on placebo demonstrated mycological cure at the end of treatment and 67% of Lamisil treated patients had negative mycological results at the end of follow up. Given the above response rates, 2 weeks therapy of Lamisil should be the minimum duration of treatment period and approximately half of the patients would require 3- 4 weeks of treatment to achieve cure.

Two double blind, controlled studies compared Lamisil 125 mg b.i.d. to placebo (39-40OR) and to griseofulvin 250 mg b.i.d. (20OR) in the treatment of *Tinea pedis*. Both studies recruited patients with chronic, recurrent disease. In the study 39-40OR, 65% of patients on Lamisil reported mycological cure at follow up whereas none of the placebo treated patients responded. In the study 20OR, Lamisil was shown to be highly effective with 88% of cure at follow up after 6 weeks therapy compared to 45% of patients on griseofulvin. These patients when observed after 10 months reported 94% cure rate, compared to 30% efficacy of griseofulvin in the same patient population.

Table 12-1 Major efficacy studies – *Tinea corporis/cruris*, *Tinea pedis*, Candida infections

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

	placebo							
20OR	6wk 125 b.i.d. DB-Griseofulvin	Lamisil 125 b.i.d Griseofulvin 250 b.i.d	16 12	2 6	94 27	100 55	75 27	88 45

Non-clinical safety data

Repeat dose toxicity

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/day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a 32-week repeated dose study in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic effect level 50 mg/kg/day). 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. In 4-week studies, intravenous administration of terbinafine resulted in central nervous system disturbances including hypoactivity, ataxia and convulsions in rats ($\geq$ 30 mg/kg/day) and monkeys (75 mg/kg/day).

Mutagenicity and carcinogenicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.

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/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/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.

Reproductive toxicity

In a fertility and reproductive study, rats were treated orally with terbinafine (10, 50, or 250 mg/kg/day) starting 9 weeks (males) or 2 weeks (females) prior to mating and continued through pregnancy and lactation. There were no effects on fertility or general reproductive performance. However, at 250 mg/kg/day (corresponding to 10 times the MRHD based on BSA), there was evidence of parental toxicity (reduced body weight gain, lower pregnancy rate and litter size), increased pre- and perinatal offspring mortality, and retarded postnatal offspring development. For information on embryofetal and pre- and postnatal toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

Juvenile animal studies
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 ≥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.

5.2 Pharmacokinetic properties

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 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.

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%

5.3 Preclinical safety data

Repeat dose toxicity
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/day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a 32-week repeated dose study in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic effect level 50 mg/kg/day). 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. In 4-week studies, intravenous administration of terbinafine resulted in central nervous system disturbances including hypoactivity, ataxia and convulsions in rats ($\geq$ 30 mg/kg/day) and monkeys (75 mg/kg/day).

Mutagenicity and carcinogenicity
A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.

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/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/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.

Reproductive toxicity
In a fertility and reproductive study, rats were treated orally with terbinafine (10, 50, or 250 mg/kg/day) starting 9 weeks (males) or 2 weeks (females) prior to mating and continued through pregnancy and lactation. There were no effects on fertility or general reproductive performance. However, at 250 mg/kg/day (corresponding to 10 times the MRHD based on BSA), there was evidence of parental toxicity (reduced body weight gain, lower pregnancy rate and litter size), increased pre- and perinatal offspring mortality, and retarded postnatal offspring development (see section 4.6).

Juvenile animal studies
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 ≥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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lamisil 125 mg tablets
Magnesium stearate
Hypromellose
Microcrystalline cellulose
Lactose
Sodium starch glycolate

Lamisil 250 mg tablets
Magnesium stearate
Silica colloidal anhydrous
Hypromellose
Microcrystalline cellulose
Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

ALU/PVC blister containing 7, 14 or 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling of the product

Lamisil 125 mg tablets
Pediatrics
The scored tablets are divisible for dosing in children according to body weight (see section 4.2).

Lamisil 250 mg tablets
Not applicable.

7. MARKETING AUTHORISATION HOLDER

Novartis Pharma AG
Lichtstrasse 35
4056 Basel
Switzerland

Manufacturer
Novartis Pharma Produktions GmbH
Oeflingerstrasse 44
79664
Wehr
Germany

8. MARKETING AUTHORISATION NUMBER

Prescription only medication.

Lamisil 125 mg tablets
Kenya : 7804

Lamisil 250 mg tablets
Kenya: 7805

9. DATE OF FIRST AUTHORISATION

Lamisil 125 mg tablets
Kenya: 15 April 1993

Lamisil 250 mg tablets
Kenya: 15 April 1993

10. DATE OF REVISION OF THE TEXT

June 2025 (CDS)