PRODUCT MONOGRAPH

Pr LAMISIL®

Terbinafine tablets 250 mg (as terbinafine hydrochloride)
Terbinafine hydrochloride topical cream 1% w/w (10 mg/g)
Terbinafine hydrochloride topical spray solution 1% w/w (10 mg/g)

Antifungal Agent

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Dorval, Quebec
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Table of Contents

Pr LAMISIL®

(terbinafine hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablets 250 mg terbinafine (as terbinafine hydrochloride)	carboxymethyl starch *(For a complete listing see Dosage Forms, Composition and Packaging)*
Topical	topical cream 1% terbinafine hydrochloride 1% w/w (10 mg/g)	*(For a complete listing see Dosage Forms, Composition and Packaging)*
Topical	topical spray solution 1% terbinafine hydrochloride 1% w/w (10 mg/g)	*(For a complete listing see Dosage Forms, Composition and Packaging)*

INDICATIONS AND CLINICAL USE

LAMISIL (terbinafine) is indicated in the treatment of fungal infections of the skin and nails caused by dermatophytes such as *Trichophyton* (e.g. *T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum*), *Microsporum canis, Epidermophyton floccosum* and yeasts of the genus *Candida* (eg. *C. albicans*), as well as *Malassezia furfur*.

Oral LAMISIL

Oral LAMISIL is indicated in the treatment of onychomycosis (fungal infection of the nail) caused by dermatophyte fungi.

Prior to initiating treatment with LAMISIL Tablets, appropriate nail or skin specimens should be obtained for laboratory testing (KOH preparation, fungal culture, or nail biopsy) in order to confirm the diagnosis of onychomycosis or dermatomycosis.

Oral LAMISIL may be considered for the treatment of severe tineal skin infections (tinea corporis, tinea cruris and tinea pedis) which have been unresponsive to topical treatment.

Note: Oral LAMISIL is not effective in pityriasis versicolor (also known as *Tinea versicolor*).

Topical LAMISIL

Cream

LAMISIL cream is indicated in the treatment of fungal infections of the skin caused by dermatophytes such as trichophyton, as well as yeast infections of the skin, principally those caused by the genus Candida (e.g. Candida albicans).

LAMISIL cream is also indicated in the treatment of pityriasis (tinea) versicolor due to Malassezia furfur.

Spray

LAMISIL spray is indicated in the treatment of fungal infections of the skin caused by dermatophytes such as trichophyton.

LAMISIL spray is also indicated in the treatment of pityriasis (tinea) versicolor due to Malassezia furfur.

Note: Topical LAMISIL is not effective in onychomycosis.

CONTRAINDICATIONS

LAMISIL (terbinafine) is contraindicated in patients with a known hypersensitivity to terbinafine or to any of the excipients of LAMISIL or component of the container. (see **DOSAGE FORMS, COMPOSITION and PACKAGING**).

LAMISIL (terbinafine hydrochloride) tablets are contraindicated for patients with chronic or active hepatic disease. (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**).

WARNINGS AND PRECAUTIONS

Oral LAMISIL

Serious Warnings and Precautions

LAMISIL (terbinafine hydrochloride) Tablets are contraindicated in patients with pre-existing chronic or active hepatic disease. Serious and life-threatening hepatic adverse reactions (including hepatic failure leading to death and liver transplant) have been reported in patients with or without pre-existing chronic or active hepatic disease receiving LAMISIL Tablets for the treatment of onychomycosis and dermatomycosis.

Baseline liver function test should be recommended before initiating treatment with LAMISIL Tablets. LAMISIL Tablets should be discontinued if biochemical or clinical evidence of liver injury

develops. (See Hepatic section below)

Hepatic

LAMISIL (terbinafine hydrochloride) Tablets are contraindicated for patients with chronic or active hepatic disease. Before prescribing LAMISIL Tablets, a baseline liver function test should be performed to assess any pre-existing liver disease since hepatotoxicity may occur in patients with and without pre-existing liver disease. 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. Patients prescribed LAMISIL Tablets should be warned to report immediately to their physician any symptoms of persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine or pale feces. Patients with these symptoms should be advised to discontinue taking oral terbinafine, and the patient's hepatic function should be immediately evaluated. (See **Laboratory Monitoring** and **ADVERSE REACTIONS**).

Renal

The pharmacokinetics of LAMISIL have been investigated in patients with renal impairment (creatinine clearance ≤ 50 mL/ min); based on this study the use of LAMISIL in renally impaired patients is not recommended (see ***CLINICAL PHARMACOLOGY*, Pharmacokinetics**).

Metabolism

In vitro and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolized by this enzyme, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), β-blockers, selective serotonine reuptake inhibitors (SSRIs), antiarrhythmics class 1A, 1B and 1C and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed up, if the co-administered drug has a narrow therapeutic window (see **DRUG INTERACTIONS**).

Skin

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 postmarketing setting.

Ophthalmologic

Changes in the ocular lens and retina have been reported following the use of LAMISIL Tablets in controlled trials. The changes noted were non-specific and the significance of these changes is unknown.

Immune

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using LAMISIL therapy for greater than six weeks.

Lupus erythematosus:

During post-marketing experience, precipitation and exacerbation of cutaneous and systemic lupus erythematosus have been reported infrequently in patients taking LAMISIL. LAMISIL therapy should be discontinued in patients with clinical signs and symptoms suggestive of lupus erythematosus.

Hematologic

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.

Neurologic, Special Senses

Sensory disturbances

Disturbances of visual, auditory and tactile senses have been reported (see **ADVERSE REACTIONS**). If visual or hearing disturbances occur, LAMISIL Tablets should be discontinued.

Taste Disturbance Including Loss of Taste

Taste disturbance, including taste loss, has been reported with the use of LAMISIL Tablets. It can be severe enough to result in decreased food intake, weight loss, and depressive symptoms. Taste disturbance usually resolves within several weeks after discontinuation of treatment.
Isolated cases of prolonged taste disturbances have also been reported. If symptoms of a taste disturbance occur, LAMISIL Tablets should be discontinued.

Smell Disturbance Including Loss of Smell

Smell disturbance, including loss of smell, has been reported with the use of LAMISIL Tablets. Smell disturbance may resolve after discontinuation of treatment, but may be prolonged (greater than one year), or may be permanent. If symptoms of a smell disturbance occur, LAMISIL Tablets should be discontinued.

Psychiatric

Anxiety and depressive symptoms

Anxiety and depressive symptoms have occurred during postmarketing use of terbinafine secondary to taste disturbances, as well as independent of taste disturbances. If depressive symptoms occur, LAMISIL Tablets should be discontinued.

Carcinogenesis and Mutagenesis

An increase in liver tumors was observed in male rats at the highest dose level (69 mg/kg) during a life-time (123 weeks) carcinogenicity study. The changes included increased enzyme activity, peroxisome proliferation and altered triglyceride metabolism. The changes have been shown to be species specific since they were not seen in mice or monkeys.

Laboratory Monitoring

Measurement of serum transaminases (ALT and AST) is advised for all patients before taking LAMISIL Tablets.

Topical LAMISIL

LAMISIL cream and spray are for external use only. LAMISIL topical formulations may be irritating to the eyes. Contact with the eyes should be avoided. LAMISIL spray should not be used on the face.

In the case of accidental ocular contact, the eyes should be rinsed thoroughly with running water and patients should consult a physician if any symptoms persist. In case of accidental inhalation, patients should be advised to consult a physician if any symptoms develop and persist.

LAMISIL spray should be used with caution in patients with lesions where alcohol could be irritating.

Local skin reactions

LAMISIL Cream contains cetyl alcohol and stearyl alcohol which may cause local skin reactions (e.g contact dermatitis).

LAMISIL Spray Solution contains propylene glycol which may cause skin irritation.

General:

Special Populations

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 suggest special recommendations for women of child-bearing potential.

Pregnant Women: Animal fetal toxicity studies did not reveal any teratogenic or embryofetotoxic potential of terbinafine. However, there is only very limited documented clinical experience with LAMISIL (terbinafine) in pregnant women; therefore, unless the potential benefits outweigh any potential risks, oral LAMISIL or LAMISIL cream should not be used during pregnancy.

Nursing Women: Terbinafine is excreted in breast milk; therefore mothers receiving oral treatment with LAMISIL should not breast feed. However, with LAMISIL cream and spray treatment, the small amounts absorbed through the skin are unlikely to affect the infant. Nursing mothers should NOT apply LAMISIL topical formulations to the breast. In addition, infants must not come into contact with any treated skin area, including the breasts.

Fertility: No effect of terbinafine on fertility has been seen in animal studies (see section **TOXICOLOGY**) and there are no data to suggest an effect on fertility in humans.

Geriatrics: Plasma concentrations and drug half-life appear to be slightly higher in elderly patients than in the general population. In addition, the incidence of all adverse events in a Post Marketing Surveillance study appeared to be slightly higher in the elderly at normal adult doses; however, the overall rate of adverse events possibly or probably related to terbinafine did not appear to be different compared to the general population. When prescribing tablets for patients in this age group, the

possibility of pre-existing impairment of liver or kidney function should be considered (see **PHARMACOKINETICS - Oral LAMISIL**).

Pediatrics: The safety and efficacy of LAMISIL have not been established in pediatric patients.

LAMISIL should be kept out of the reach of children.

Occupational Hazards

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 REACTIONS

Adverse Drug Reaction Overview

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Frequency estimate: very common ≥ 10%, common ≥ 1% to < 10%, uncommon ≥ 0.1% to < 1%, rare ≥ 0.01% to < 0.1%, very rare <0.01% (includes isolated reports).

Clinical Trials Adverse Drug Reactions

LAMISIL tablets

Serious and life-threatening hepatic adverse reactions, including fatal outcome or requiring liver transplant, have been reported in patients receiving LAMISIL Tablets.

In clinical trials submitted for purposes of marketing approval in Canada adverse events occurred in 10.4% of patients receiving the recommended oral dose. Of these, 5% were mild to moderate gastrointestinal events (abdominal distension, decreased appetite, dyspepsia, nausea, mild abdominal pain, diarrhea), 3% were rash, urticaria and the remainder were for musculoskeletal reactions (arthralgia, myalgia) and miscellaneous non-specific events such as malaise or tiredness.

The following table of adverse events illustrates some of these results:

TABLE I

Organ System Adverse Event	LAMISIL 250 mg (n = 998)	
	Number	(%)
SKIN (overall)	27	2.7%
Erythema or rash	9	0.9
Urticaria	5	0.5
Eczema	1	0.1
Pruritis	4	0.4
Other	8	0. 8
GI (overall)	52	5.2
Diarrhea and/or cramps	10	1.0
Nausea and/or vomiting	11	1.1
Fullness	5	0.5
Sickness	1	0.1
G.I. irritation, dyspepsia, gastritis	22	2.2
Other	3	0.3
CNS (overall)	12	1.2
Headache	9	0.9
Concentration	2	0.2
Other	1	0.1
OTHER (overall)	11	1.1
Tiredness, fatigue	3	0.3
Pain (back, knee, legs, feet, kidney)	1	0.1
Change of taste or dry mouth	1	0.1
Other	6	0.6
LABORATORY ADVERSE CHANGES (overall)	2	0.2
Hypoglycemia	1	0.1
Elevated Liver enzymes	1	0.1
TOTAL	104	10.4

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events not frequently observed include the following:

Uncommon: Paresthesia and hypoesthesia

Rare: Idiosyncratic and symptomatic hepatobiliary reactions (2/3 primarily cholestatic in nature and the remainder involving hepatocytic damage or both) have been reported in association with LAMISIL treatment, including very rare cases of serious hepatic failure (some leading to liver transplant or death). Unspecific prodromal symptoms (nausea, anorexia, fatigue, general malaise) have been reported. Liver enzyme increases have been noted in asymptomatic patients as well as in patients with more

specific symptoms of hepatic dysfunction (jaundice, upper abdominal right quadrant pain, pruritus, pale stools, dark urine). Hepatic failure, hepatitis, jaundice, cholestasis, hepatic enzyme increased (see **WARNINGS AND PRECAUTIONS**).

The frequency of reported apparent hepatic dysfunctions has varied. An analysis of 7 key placebo-controlled trials (262 placebo vs 1624 LAMISIL patients) suggested increases of 1.4% vs 3.4% in liver function test indicators (APase, SGPT (AST), SGOT (ALT), g-GT, bilirubin >2x above upper normal). In a European post-marketing study in 25 884 patients, asymptomatic liver enzyme increases were reported in 0.17% of patients treated. The reporting frequency for symptomatic liver disorder possibly related to LAMISIL was 1:13 000. The relative risk of acute liver injury in this group was considered to be 4.2 times the background incidence.

In the less controlled circumstances of spontaneous worldwide reporting, the development of clinically significant signs and symptoms of hepatobiliary dysfunction for which no other cause was apparent, and in which LAMISIL was considered the possible causative agent, was calculated to be approximately 1:37 000 treated patients. The reporting frequency overall for hepatobiliary events including elevations in liver enzymes was 1:15 000. Very rare cases of liver failure, some fatal, have been associated with LAMISIL treatment and the incidence rate is about 1:1 000 000 exposed patients.

LAMISIL cream and spray

Local symptoms such as pruritus, skin lesion, skin disorder, skin exfoliation, application site pain, application site irritation, pigmentation disorder, skin burning sensation, erythema, scab, dry skin, dermatitis contact, eczema may occur at the site of application; however, treatment rarely has to be discontinued for this reason. These minor symptoms must be distinguished from allergic reactions (e.g. bullous eruptions, hives, widespread rash and/or redness, urticaria, angioedema, or positive rechallenge) which are rare but require discontinuation of the drug. In clinical trials, adverse reactions were recorded in 33 of the 1757 (1.8%) patients who received LAMISIL cream, and in 39 of the 898 (4.3%) patients who received LAMISIL spray.

Post-Market Adverse Drug Reactions

LAMISIL tablets

The following adverse drug reactions have been identified based on post-marketing spontaneous reports with LAMISIL tablets and are organized by system organ classes. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and lymphatic system disorders: neutropenia, agranulocytosis, thrombocytopenia, anemia, pancytopenia, thrombocytopenic purpura (TPP). The mechanism of TPP induction and the role of LAMISIL have not been elucidated.

Hepatobiliary disorders: Cases of hepatic failure some leading to liver transplant or death and, idiosyncratic and symptomatic hepatic injury. Cases of hepatitis, cholestasis, and increased hepatic enzymes have been seen with the use of LAMISIL Tablets.

Immune system disorders: anaphylactic reaction including anaphylactic shock, respiratory compromised symptoms such as dyspnea, angioedema, serum sickness-like reaction, skin reactions (see Skin section), precipitation or exacerbation of cutaneous or systemic lupus erythematosus

Psychiatric disorders: anxiety and depressive symptoms secondary to taste disturbances. Anxiety and depressive symptoms independent of taste disturbance have also been reported with use of LAMISIL Tablets.

Eye disorders: visual impairment, vision blurred, visual acuity reduced.

Ear and labyrinth disorders: hypoacusis, impaired hearing, tinnitus.

Vascular disorders: vasculitis.

Nervous system disorders: dizziness, anosmia including permanent anosmia, hyposmia. Dysgeusia including ageusia (hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported)

Gastrointestinal disorders: pancreatitis.

Musculoskeletal and connective tissue disorders: rhabdomyolysis, arthritis.

General disorders and administration site conditions: influenza-like illness, pyrexia.

Investigations: blood creatine phosphokinase increased, weight decreased (secondary to dysgeusia)

Skin and subcutaneous tissue disorders: Stevens Johnson syndrome, Toxic Epidermal Necrolysis,

erythema multiforme, acute generalized exanthematous pustulosis, toxic skin eruption, dermatitis exfoliative, dermatitis bullous, psoriasiform eruptions or exacerbation of psoriasis, photosensitivity reactions (e.g. photodermatosis, photosensitivity allergic reaction and polymorphic light eruption) and alopecia.

DRUG INTERACTIONS

Overview

Tablets: Many categories of drugs are known to inhibit or induce drug metabolism by cytochrome P450 (CYP) enzymes located in the liver and intestine. Co-administration of such drugs may impact metabolic elimination of drugs, and in some cases, bioavailability may be either increased or decreased and accordingly, possibly necessitate dosage adjustments (See **ACTION AND CLINICAL PHARMACOLOGY, Metabolism and Excretion**).

Drug-Drug Interactions

Effects of other medicinal products on terbinafine:

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, in a randomized, open-label, single-dose, three-period crossover study (7 day washout) in healthy male adult subjects (n = 18), treated with 750 mg terbinafine, 100 mg fluconazole and 750 mg terbinafine plus 100 mg fluconazole. The interaction likely involves inhibition of CYP2C9 and CYP3A4 enzymes.

Theophylline increased the Cmax and AUC of terbinafine by 25% each, and decreased the oral clearance of terbinafine by 24% in a randomized, open-label, single-dose, three-period crossover study, in healthy male and female adult subjects (n = 18) treated orally with 250 mg terbinafine, 375 mg theophylline, and 250 mg terbinafine plus 375 mg theophylline.

Ketoconazole may increase the systemic exposure to terbinafine, based on predicted inhibition of CYP2C9 and CYP3A4 (no studies were performed).

Amiodarone may increase the systemic exposure to terbinafine, based on predicted inhibition of CYP2C9 and CYP3A4 (no studies were performed).

Cotrimoxazole (trimethoprim sulfamethoxazole) did not alter the pharmacokinetics of terbinafine, in a randomized, open-label, single-dose, three-period crossover study (7 day washout) in healthy male and female adult subjects (n = 18), treated with 750 mg terbinafine, 160 mg trimethoprim plus 800 mg sulfamethoxazole, and 750 mg terbinafine plus 160 mg trimethoprim plus 800 mg sulfamethoxazole.

Zidovudine did not alter the pharmacokinetics of terbinafine, in a randomized, open-label, single-dose, three-period crossover study (7 day washout) in healthy male and female adult subjects (n = 18), treated with 750 mg terbinafine, 200 mg zidovudine, and 750 mg terbinafine plus 200 mg zidovudine.

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 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.

Terbinafine did not alter the pharmacokinetics of fluconazole in a randomized, open-label, single-dose, three-period crossover study (7 day washout) in healthy male adult subjects, treated with 750 mg terbinafine, 100 mg fluconazole and 750 mg terbinafine plus 100 mg fluconazole.

Terbinafine did not alter the pharmacokinetics of cotrimoxazole (trimethoprim and sulfamethoxazole), in a randomized, open-label, single-dose, three-period crossover study (7 day washout) in healthy male and female adult subjects (n = 18), treated with 750 mg terbinafine, 160 mg trimethoprim plus 800 mg sulfamethoxazole, and 750 mg terbinafine plus 160 mg trimethoprim plus 800 mg sulfamethoxazole.

Terbinafine reduced zidovudine Cmax by 25%, increased AUC by 15%, reduced oral clearance by 15% and did not alter zidovudine plasma elimination half-life, in a randomized, open-label, single-dose, three-period crossover study (7 day washout) in healthy male and female adult subjects (n = 18), treated with 750 mg terbinafine, 200 mg zidovudine, and 750 mg terbinafine plus 200 mg zidovudine.

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.

Single dose terbinafine did not significantly alter the pharmacokinetics of theophylline in a randomized, open-label, single-dose, three-period crossover study, in healthy male and female adult subjects (n = 18) treated orally with 250 mg terbinafine, 375 mg theophylline, and 250 mg terbinafine plus 375 mg theophylline.

Multiple dose terbinafine increased the AUC and half-life of theophylline by 16% and 24%, respectively, and decreased the oral clearance of theophylline by 14%, in a randomized, open-label, two-period crossover study in healthy male and female adult subjects (n = 12) treated orally with a single dose of 5 mg/kg theophylline alone (mean 345 mg, range 307 to 397 mg) and 2 hours after the last of 4 daily doses of 250 mg terbinafine.

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 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 serotonine reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, particularly if they also have a narrow therapeutic window (see **WARNINGS AND PRECAUTIONS**). Case reports indicating interactions of LAMISIL with tricyclic antidepressants e.g nortriptyline and imipramine) have been reported in a post-marketing setting.

Terbinafine decreased the clearance of desipramine by 82%.

Terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average, in healthy subjects, converting some extensive CYP2D6 metabolizers to poor metabolizer status after treatment with 250 mg terbinafine once daily for 14 days.

The effect of terbinafine on the dextromethorphan/dextrorphan metabolic ratio in urine was shown to be reversible, though the interaction potential may last for several weeks after termination of a

LAMISIL treatment cycle.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products:

Terbinafine increased the clearance of ciclosporin by 15%.

Cream and spray:

No drug interactions are known to date.

Drug-Herb Interactions

St John's wort may considerably decrease the plasma concentration and exposure of terbinafine, however the extent of decrease in exposure is not known.

DOSAGE AND ADMINISTRATION

ORAL

LAMISIL tablets

Adults: 250 mg once daily (See also **DOSING CONSIDERATIONS**).

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.

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

TABLE II

Indication	Duration of Treatment
Onychomycosis (of fingers and toes)*	6 weeks to 3 months
Skin Infections** Tinea pedis (interdigital & plantar/moccasin type)	2-6 weeks
Tinea corporis, cruris	2-4 weeks

* In patients with fingernail infections or toenail infections other than the big toe, or in younger patients, treatment periods of less than 3 months may be adequate. In patients with infections of the big toenail, treatment for 3 months is usually sufficient, although some patients may require treatment for 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. In onychomycosis 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 tissue.

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

TOPICAL

LAMISIL cream

LAMISIL cream can be applied once or twice daily depending on the indication. The affected areas should be cleansed and dried thoroughly before application of LAMISIL. The cream should be applied to the affected skin and surrounding area in a thin layer and rubbed in lightly. In the case of intertriginous infections (submammary, interdigital, intergluteal, inguinal) the area to which the cream has been applied may be covered with a gauze strip, especially at night.

The duration and frequency of treatment varies with the indication and is dependent on the severity of the infection:

TABLE III

Indication	Duration of Treatment
Tinea pedis	1 week , once a day
Tinea corporis/cruris	1 week , once a day
Cutaneous Candidiasis	1 to 2 weeks once or twice a day *
Pityriasis versicolor	2 weeks, once or twice a day

* Two weeks of treatment with LAMISIL cream produced slightly improved efficacy over treatment for one week. The difference in outcome may not be clinically significant.

Many patients treated with shorter durations of therapy (1-2 weeks) continue to improve during the 2-4 weeks after therapy has been completed. As a consequence, patients should not be considered therapeutic failures until they have been observed for a period of 2-4 weeks after cessation of treatment.

Relief of clinical symptoms usually occurs within a few days. Irregular use or premature discontinuation of treatment increases the risk of recurrence. If there are no signs of improvement after two weeks the diagnosis should be verified.

LAMISIL spray

LAMISIL spray is applied once or twice daily, depending on the indication. The affected areas should be cleansed and dried thoroughly before application of LAMISIL. A sufficient amount of solution should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area (See **WARNINGS AND PRECAUTIONS**).

The duration of treatment varies with the indication and is dependent on the severity of the infection:

TABLE IV

Indication	Duration of Treatment
Tinea pedis	1 week, once a day
Tinea corporis/cruris	1 week, once a day
Pityriasis versicolor	1 week, twice a day

Relief of clinical symptoms usually occurs within a few days. Irregular use or premature discontinuation of treatment increases the risk of recurrence. If there are no signs of improvement after two weeks the diagnosis should be verified.

DOSING CONSIDERATIONS

Special populations:

Liver impairment

LAMISIL tablets are contraindicated for patients with chronic or active ~~liver~~hepatic ~~-~~disease (see **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 **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

A few cases of overdosage with LAMISIL tablets (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.

No case of overdosage has been reported with LAMISIL cream and spray. The low systemic absorption of topical terbinafine renders overdosage extremely unlikely. Accidental ingestion of one 30 g tube of LAMISIL cream or one 30 mL bottle of LAMISIL spray, which contain 300 mg terbinafine, is comparable to one LAMISIL 250 mg tablet. However, should, larger amounts of topical LAMISIL be inadvertently ingested, adverse effects similar to those observed with an overdosage of LAMISIL tablets are to be expected (e.g. headache, nausea, epigastric pain and dizziness). The alcohol content of the spray (28.8% v/v) has to be taken into account.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LAMISIL (terbinafine) is an allylamine which has a broad spectrum of antifungal activity. At low concentrations LAMISIL is fungicidal against dermatophytes, molds and certain dimorphic fungi. Its activity against yeasts is fungicidal or fungistatic, depending on the species.

Pharmacodynamics

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.

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

Pharmacokinetics

Oral *LAMISIL*

Absorption: Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from LAMISIL tablets as a result of first-pass metabolism is approximately 50 %. A single 250 mg dose of LAMISIL tablets resulted in mean peak plasma concentration of 1.3 μg/ml within 1.5 hours after 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. 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 dosing adjustments.

Distribution: LAMISIL binds strongly to plasma proteins (99%) and is lipophilic. LAMISIL is widely distributed in the body including adipose tissue. It rapidly diffuses through the dermis and accumulates in lipophilic stratum corneum. It is also secreted in sebum, thus achieving high

concentrations in hair follicles, hair and sebum-rich skin. There is evidence that LAMISIL is distributed in the nail plate within the first few weeks of commencing therapy.

Metabolism and Excretion: Oral LAMISIL is excreted mainly in urine (80%) and in feces (20%). Following absorption terbinafine is metabolized rapidly and extensively by the liver. At least seven cytochrome isoenzymes are involved in its metabolism with major contributions from CYP 2C9, CYP 1A2, CYP 3A4, CYP 2C8 and CYP 2C19. Biotransformation results in metabolites with no antifungal activity which are excreted predominantly through the urine. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been observed. Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days

Following a single 250 mg dose in 12 hepatically impaired cirrhotic (alcoholic) patients, total clearance of terbinafine was reduced by about 40%. In a sample of 12 renally impaired patients (median creatinine clearance of 17.6 mL/min), LAMISIL clearance following a single 250 mg dose was halved resulting in the doubling or more of peak plasma concentrations or AUC. Patients at the highest and lowest ends of the renal impairment spectrum were not represented. There was no direct correlation between creatinine clearance and terbinafine clearance in renally impaired patients, the metabolism of the drug having been impaired in these patients due to competition between metabolite and parent drug.

Topical LAMISIL

Less than 5% of the dose is absorbed after topical application to humans; systemic exposure is thus very slight.

STORAGE AND STABILITY

Store at temperatures between 15° and 30°C.

SPECIAL HANDLING INSTRUCTIONS

Protect tablets from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

	Tablets	Cream	Spray
Dosage Form	250 mg	1% cream	1% spray
Description	Whitish to yellow tinged white, circular, biconvex, with bevelled edges tablet, scored on one side and embossed "LAMISIL 250"	White, smooth or almost smooth, glossy cream with a weak characteristic odor	Colourless to faintly yellow clear liquid
Composition	Terbinafine 250 mg (as terbinafine hydrochloride); magnesium stearate, hypromellose, silica colloidal anhydrous, sodium starch glycollate cellilose microcrystalline granulate.	Terbinafine hydrochloride 1% w/w; benzyl alcohol; cetyl alcohol; cetyl palmitate; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; stearyl alcohol.	terbinafine hydro-chloride 1% w/w; ceto-macrogol 1000; ethanol (28.8% v/v); propylene glycol; water.
Packaging	Bottle of 100 and 500 tablets. Blister packs of 28 tablets (14 tablets per blister).	15 or 30 gram tubes	30 mL bottles

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

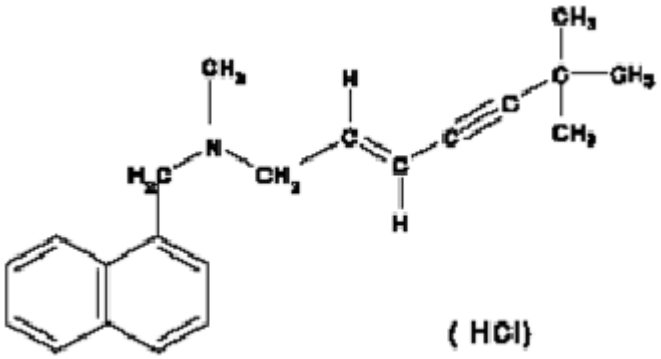
Drug Substance

Proper Name: INN, BAN, USAN: terbinafine

Chemical Name: (E)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl-1-naphthaline-methanamine (-hydrochloride)

Molecular Formula/Mass:
Terbinafine base: 291.40
Terbinafine Hydrochloride: $C_{21}H_{26}NCl$/327.90

Structural formula:



Physicochemical properties:

- white to off-white finely crystalline powder
- melting point: ~ 205°C.
- pKa (I) value: 7.10
- pH of a solution (0.5%) in methanol/water 4:6 (V/V): ~ 4.7. at 25°C.
- Solubility: 0.63% (W/V) in water and >2% (W/V) in chloroform

CLINICAL TRIALS

ORAL†

Onychomycosis

Two studies evaluated the efficacy of oral terbinafine in the treatment of toe or fingernail onychomycosis.

Study Demographics and Trial Design

Summary of patient demographics for oral terbinafine clinical trials in onychomycosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race
SF1501	Randomized, double-blind (double-dummy), multicenter, parallel group,stratified enrolment (toe/fingernail) b.i.d. vs o.d. dosage	Terbinafine tablets, oral 125 mg b.i.d up to 48 wk (toenail) or 24 wk (fingernail)	51 enrolled 43 evaluable	45 (18-74)	Male = 34 Female = 9	Not reported
		Terbinafine tablets, 2x125 mg o.d. up to 48 wk (toenail) or 24 wk (fingernail)	52 enrolled 48 evaluable	45 (18-74)	Male = 34 Female = 14	Not reported
SF00423	Randomized, double-blind, multicenter, parallel group, griseofulvin-comparative	Terbinafine capsules: Oral, 250 mg bid for 3-6 months	47 enrolled 29 evaluable	44.6 (21-76 yr)	Male = 24	Caucasian 100%
		Griseofulvin capsules: Oral 250 mg bid for up to 6 months (standard treatment period is up to 12 months)	34 enrolled 22 evaluable	43.5 (20-61 yr)	Male = 15	Caucasian 100%

Study Results

Results of study SF1501 in onychomycosis

Primary Endpoints	b.i.d. Number (%) patients	o.d. Number (%) patients
Mycological cure (negative KOH and culture) – all infections	Toenails	
	25/31 (81%)	28/35 (80%)
	Fingernails	
	10/10 (100%)	10/11 (91%)
Effective treatment (negative mycology plus continuous or limited nail growth) at end of treatment at week 24 - all infections	Toenails	
	24/32 (75%)	26/37 (70%)
	Fingernails	
	10/11 (91%)	10/11 (91%)

There were no significant differences between b.i.d and o.d. treatment regimens with respect to mycological cure rates or rates of effective treatment. Mycological cure at end of treatment was 95 % for fingernails and 80% for toenails. At follow-up visit 3-12 months later, over 81% of toenail onychomycosis were cured without relapse.

Results of study SFO0423 in onychomycosis

Primary Endpoints	**Terbinafine Number (%) patients**	**Comparator Number (%) patients**
Effective treatment (negative mycology plus continuous or limited nail growth) at end of treatment at week 24*	Toenail	
	11/20 (55%)	5/12 (42%)
	Fingernail	
	7/9 (78%)	8/10 (80%)
Mycological cure (negative culture and KOH) at week 24	Toenail	
	12/20 (60%)	5/12 (42%)
	Fingernail	
	7/9 (78%)	7/10 (70%)

*The combined clinical/mycological endpoint was not specified in the protocol

Effective treatment in the LAMISIL treated group was 78% fingernail and 55% toenail with treatment durations of 3-6 months. Griseofulvin was 80% and 42% effective for fingernails and toenails respectively. Thus, short duration therapy (3-6 months) using 500 mg per day of LAMISIL appears effective in many patients with onychomycosis due to dermatophyte infections.

Tinea corporis/cruris

Study demographics and trial design

Summary of patient demographics for oral terbinafine clinical trials in tinea corporis/cruris

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age across studies (Range)**	**Gender**	**Race: Percent Caucasian**
Placebo-controlled: SFO041B 5-OR SFO041C	Randomized, single or multicenter, parallel group, double-blind, placebo controlled	Terbinafine oral, capsules, 125 mg bid for 4 wk; 2 wk follow-up	Entered 79 Evaluable 62	34 - 40 years (18-74)	Male = 50 Female 11	71-100%
		Matching placebo	Entered 77 Evaluable 62	37-42 (18-70)	Male = 49 Female = 13	
Griseofulvin-controlled: 11-OR SFO044	Randomized, single or multicenter, parallel group, double-blind, double-dummy, griseofulvin-controlled	Terbinafine oral capsules, 125 mg and placebo bid for up to 6 wk; 2-6 wk follow-up	Entered 189 Evaluable 174	37-38 (17-69)	Male = 105 Female = 69	85-99%

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
		Griseofulvin oral capsules 2x250 mg bid for up to 6 wk; 2-6 wk follow-up	Entered 192 Evaluable 170	31-34 (17-85)	Male = 107 Female = 63	
Ketoconazole controlled: **SF3006** **SF0047**	Randomized, single or multicenter, parallel group, double-blind, double-dummy, griseofulvin-controlled	Terbinafine oral capsules, 125 mg and placebo bid for up to 6 wk; 4-8 wk follow-up	Entered 73 Evaluable 65	34-48 (18-80)	Male = 40 Female = 25	60-92%
		Ketoconazole oral capsules 200 mg od (placebo od) for up to 6 wk; 2-6 wk follow-up	Entered = 71 Evaluable = 62	31-43 (16-70)	Male = 40 Female = 22	

Study results

Combined results of placebo-controlled studies SF 0041 B, 5-OR, SF 0041C in tinea corporis/cruris[1]

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)
Mycological cure (negative culture and KOH) at follow-up	7-30 (100 - 64%)	0-4 (0-36%)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	8-30 (62-91%)	0-4 (0-23%)
5-OR: mycological cure results (combined culture and KOH results) were not provided and too few patients returned at follow-up for meaningful assessments. However, at end of treatment, terbinafine was significantly better than placebo in terms of mycological cures and negative KOH results (Negative KOH of 73% vs 17% for active and placebo, p = 0.043; Negative cultures of 73% vs 0% for active and placebo, p = -.007) .		
SF 0041B: too few placebo patients returned at follow-up for meaningful assessments; however, at end of therapy the proportion of patients with mycological cures was greater in the terbinafine group compared with placebo; effective treatment was noted in 75% and 23% of active and placebo groups		

[1] Range of values represents the highest and lowest values noted across the studies represented

The efficacy of a up to 6 weeks of treatment with terbinafine was consistently positive across 3 placebo-controlled trials both in rates of mycological cures and in the combination of mycological and clinical endpoints. In the placebo-controlled trials, placebo patients often did not return at the post-treatment follow-up to provide meaningful results at that visit. However, results at the end of treatment speak to the high degree of efficacy of terbinafine using clinical and/or mycological endpoints. Results of 4 studies with active comparators show terbinafine to be at least as good as, if not better than, systemically administered griseofulvin and ketoconazole.

Results of griseofulvin-controlled studies 11-OR and SF 0044 in tinea corporis/cruris[1]

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Mycological cure (negative culture and KOH) at follow-up	111 - 40 (93-100%)	101- 36 (94 – 95%)

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	119 – 37 (94 – 77%)	108 – 36 (86-82%)

[1] Range of values represents the highest and lowest values noted across the studies represented

Results of ketoconazole-controlled studies SF 3006 and SF 0047 in tinea corporis/cruris[1]

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Mycological cure (negative culture and KOH) at follow-up	28-36 (100 – 97%)	23 – 31 (92-86)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	28 – 35 (100 – 95%)	23 – 29 (92 – 78 %)

[1] Range of values represents the highest and lowest values noted across the studies represented

Tinea Pedis

Study demographics and trial design

Summary of patient demographics for clinical trials in tinea pedis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race
39-40OR	Randomized, double-blind, multicenter, placebo-controlled	Terbinafine tablets (or matching placebo) 125 mg bid for 6 weeks; 2 week follow-up	Terbinafine Enrolled 26 Evaluable 23	37 years (20-64)	Male = 15 Female =8	92% Caucasian
			Placebo Enrolled 24 Evaluable 18	40 years (20-68)	Male = 13 Female=5	
SF 0508	Randomized, double-blind, multicenter, placebo-controlled	Terbinafine tablets (or matching placebo) 125x2 mg od for 2 weeks; 6 week follow-up	Terbinafine Enrolled 18 Evaluable 14	39 years (19-72)	Male = 20 Female =6	79% Caucasian
			Placebo Enrolled 19 Evaluable 14	45 years (20-82)	Male =23 Female = 4	
SF 0025	Randomized, double-blind, multicenter, griseofulvin controlled	Terbinafine capsules, 125 mg bid for 6 wk; 2 wk follow-up	Enrolled 39 Evaluable 33	38 years (18-79)	Male = 17 Female = 16	95% Caucasian
		Griseofulvin capsules 250 mg bid for 6 wk; 2 wk follow-up	Enrolled 37 Evaluable 33	35 years (14-59)	Male = 18 Female = 15	
20-OR	Randomized, double-blind, multicenter, griseofulvin controlled	Terbinafine capsules, 125 mg bid for 6 wk; 2 wk follow-up	Enrolled 18 Evaluable 16	38 years (22-63)	Male = 11 Female = 5	82% Caucasian

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race
		Griseofulvin capsules 250 mg bid for 6 wk; 2 wk follow-up	Enrolled 18 Evaluable 12	36 years (20-49)	Male = 9 Female = 3	

Study results

Results of placebo controlled studies 39-40OR, SFO508 in tinea pedis

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)
Mycological cure (negative culture and microscopy) at follow-up		
Study 39-40OR*	17/22 (77%)	0/6 (0%)
Study SF0508†	12/14 (86)%	1/14(7%)
Effective treatment (negative mycology and minimal signs and symptoms) at follow-up		
Study 39-40OR*	15/23 (65%)	0/18 (0%)
Study SF0508†	10/14 (71%)	0/14 (0%)

* Too few placebo patients at follow-up to determine
† P <0.001, Fisher Exact test, one-sided

Placebo-controlled trials demonstrated a consistent treatment effect 2-6 weeks after cessation of treatment, whether assessed solely by mycological results, or when assessed by combined mycological and clinical parameters. Both 6-week and 2-week, o.d., and b.i.d. regimens were effective. In study 39-40OR, too few placebo patients returned at the follow-up visit to allow meaningful statistical analysis of results. Mycological cures and effective treatment rates at end of the 6 week treatment period, however, were significantly greater in the terbinafine treatment group than in the placebo group.

Results of study griseofulvin-controlled studies SF 0025 and 20-OR in tinea pedis

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Mycological cure (negative culture and microscopy) at follow-up		
SF 0025*	32/33 (97%)	28/31 (90%)
20-OR*	16/16 (100%)	6/11 (55%)
Effective treatment (negative mycology and minimal signs and symptoms) at follow-up		
SF 0025†	32/33 (97%)	26/33 (79%)
20-OR†	14/16 (88%)	5/11 (45%)

* Statistical significance not reported
† p = 0.054 Fishers Exact test

Two weeks after the end of 6 week courses of treatment, two small studies showed terbinafine to be better than griseofulvin in terms of mycological or combined mycological and clinical parameters.

†**LAMISIL** 125 mg tablets are not currently available on the Canadian market.

TOPICAL - LAMISIL Cream

Tinea corporis/Tinea cruris

Study demographics and trial design

Summary of patient demographics for terbinafine cream clinical trials in tinea corporis/cruris

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
Placebo-controlled: **SF 2002** **SF 2004**	Randomized, multicenter, parallel group, double-blind, placebo controlled	Terbinafine 1% cream once daily for 1 wk; 3 wk follow-up	Entered 78 Evaluable 66	31-39 (5-89)[1]	Male 27[1] Female 9[1]	Caucasian 51-67%
		Cream vehicle	Entered 82 Evaluable 73	36-40 (6-70) [1]	Male 31[1] Female 7[1]	

[1] Range and distribution by sex provided only for SF 2002.

Study results

Combined results of placebo-controlled studies SF 2002 and SF2004, terbinafine cream 1%, in tinea corporis/cruris, 2 wk post-treatment

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)
Mycological cure (negative culture and KOH) at follow-up*	30-27 (88-93%)	5 in each study (31% in each study)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up†	26-29 (81-87%)	4-5 (11-14%)

*Study 2002, p value for mycological cure not provided; p <0.007 for KOH and culture results individually. For study 2004 p <0.001 for mycological cure

† p <0.001 for both studies

Two double-blind, placebo controlled studies evaluated whether one week of LAMISIL 1% cream was sufficient to treat Tinea corporis/cruris. At the three week follow-up LAMISIL was effective in 81% -87% of patients, clearly demonstrating the efficacy of daily short duration (one week) treatment.

Tinea Pedis

Study demographics and trial design

Summary of patient demographics for terbinafine 1% cream clinical trials in tinea pedis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
Placebo-controlled: **81 T, 4 wk** **SF0505, 2 wk** **SF0020, 4 wk**	Randomized single or multicenter, parallel group, double-blind, placebo controlled	Terbinafine 1% cream once daily for 2-4 wk	Entered 90 Evaluable 70	36-37 yr (12-72)	Male 38 Female 32	Race not quantified; majority were Mestizo
		Cream vehicle	Entered 87 Evaluable 70	38-41 yr (10-86)	Male 39 Female 31	
Clotrimazole-controlled: **SF018**	Randomized, single or multicenter, parallel group, double-blind, clotrimazole-crean controlled	Terbinafine 1% cream once daily for 4 wk; 2 wk follow-up	Entered 164 Evaluable 133	40 yr (18-76)	Male 100 Female 33	Caucasian 79%
		Clotrimazole 1% cream once daily for 4 wk; 2 wk follow-up	Entered 168 Evaluable 134	40 yr (15-88)	Male 94 Female 39	
Ketoconazole controlled **ITUK 85**	Randomized, single or multicenter, parallel group, ketoconazole-cream controlled	Terbinafine 1% cream once daily for 4 wk; 2 wk follow-up	Entered 89 Evaluable 72	38 (17-61)	Male 72 Female 0	Caucasian 96%
		Ketoconazole 2% cream once daily for 4 wk; 2 wk follow-up	Entered 89 Evaluable 73	37 (17-63)	Male 73 Female 0	

Study results

Combined results of placebo-controlled studies terbinafine 1% cream studies in tinea pedis [1]

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)	Significance
Mycological cure (negative culture and KOH) at follow-up	10-24 (67-95)	1-13 (13-60%)	Not specified for 81 T P <0.03 for others
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	9-23 (60-80%)	1-12 (7-33%)	Not specified for 81 T P <0.006 for others

[1] Range of values represents the highest and lowest values noted across the studies represented.

Combined results of active-controlled studies terbinafine 1% cream studies in tinea pedis

Primary Endpoints	Terbinafine Number (%)	Active control Number (%)
Mycological cure (negative culture and KOH) at follow-up:		
Vs clotrimazole cream	116 (91%)	98 (78%)

Vs ketoconazole cream	68 (100%)	66 (96%)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up:		
Vs clotrimazole cream	98 (75%)	79 (61)
Vs ketoconazole	61 (86%)	58 (81%)
Effective treatment at follow-up is estimated from relapse data (0 relapse for terbinafine; 2 relapses for ketoconazole)		

Cutaneous Candidiasis

Study demographics and trial design

Summary of patient demographics for terbinafine 1% cream clinical trials in cutaneous candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
SF 1003 **SF 1004**	Randomized, double-blind, single-center, vehicle controlled	Terbinafine 1% cream, once daily for 1 wk; 3 wk follow-up	Entered 69 Evaluable 63	35-40 (6 to 78)	Male 31 Female 32	Black or Mestiza and Caucasian
		Terbinafine 1% cream vehicle , once daily for 1 wk; 3 wk follow-up	Entered 67 Evaluable 63	34-37 (13-81)	Male 44 Female 19	

Study results

Combined results of vehicle-controlled studies terbinafine 1% cream studies in cutaneous candidiasis

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)	Significance
Mycological cure (negative culture and KOH) at follow-up	22-25 (86-73%)	9-11 (28-61%)	NS
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	22-23 (71-72%)	1-7 (3-23%)	P <0.001 in both studies

p-values and results for effective treatment at follow-up are based on ITT population

The efficacy of one week of once-daily treatment with terbinafine 1% cream in cutaneous candidiasis is shown by the significantly greater rate of combined mycological and clinical outcomes, even 3 weeks post-treatment. While mycological cures were not significantly different between treatment groups post-treatment, they were significantly different at the end of treatment. Even though mycological cure appeared to decrease post-treatment, the rates of clinical cure (negative mycology and minimal signs and/or symptoms) increased. In study SF1003, complete clinical cure was noted for 3 terbinafine patients at end of treatment and 15 at Week 4. In study SF1004 for the terbinafine group, there was 1 complete cure at end of treatment but 17 at Week 4. No such increase in complete cures was noted in the vehicle group.

TOPICAL - LAMISIL Spray

Tinea corporis/Tinea cruris

Study demographics and trial design

Summary of patient demographics for terbinafine 1% spray clinical trials in tinea corporis/cruris

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
SFF 303	Randomized, double-blind, vehicle controlled (2:1 terbinafine: vehicle), parallel group, multicenter	Terbinafine 1% solution once daily for 7 days; 7 wk follow-up	Entered 102 ITT 72	42 (17-84)	Male 56 Female 16	89%
		Terbinafine solution vehicle as above	Entered 49 ITT 37	45 (18-71)	Male 28 Female 9	86%
SFF 105	Randomized, double-blind, vehicle controlled, parallel group, multicenter	Terbinafine 1% solution once daily for 7 days; 3 wk follow-up	Entered 32 ITT 26	41 (9-82)	Male 17 Female 9	81%
		Terbinafine solution vehicle as above	Entered 34 ITT 26	43 (6-71)	Male 18 Female 8	77%
SFF 108	Randomized, double-blind, vehicle controlled, parallel group, multicenter	Terbinafine 1% solution once daily for 7 days; 3 wk follow-up	Entered 36 ITT 35	32 (5-76)	Male 26 Female 9	71%
		Terbinafine solution vehicle as above	Entered 36 ITT 35	37 (8-81)	Male 23 Female 12	71%

Study results

LAMISIL 1% topical solution was significantly more effective than placebo when applied once daily for one week in patients with Tinea corporis/cruris**.**

Number (%) subjects with effective treatment (ET) or with both negative microscopy and culture (NM) at study end-point

Study No.	Treatment	Results	
		ET	NM
SFF 303	LAMISIL Placebo	71% 11% p<0.001	85% 28% p<0.001
SFF 105	LAMISIL Placebo	65% 8% p<0.001	69% 23% p=0.004
	LAMISIL Placebo	65% 20% p<0.001	76% 29% p<0.001

Tinea pedis

Study demographics and trial design

Summary of patient demographics for terbinafine 1% spray clinical trials in tinea pedis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
SFF 301	Multicenter, double-blind, vehicle-controlled, 2:1 randomization (terbinafine:vehicle)	Terbinafine 1% solution once daily for 7 days; 7 wk follow-up	Entered 115 ITT 105	41 (18-81)	Male 51 Female 20	96%
		Terbinafine solution vehicle as above	Entered 57 ITT 51	42 (18-75)	Male 35 Female 4	95%
SFF 351	Multicenter, double-blind, vehicle-controlled, 2:1 randomization (terbinafine:vehicle)	Terbinafine 1% solution twice daily for 7 days; 7 wk follow-up	Entered 104 ITT 81	41 (12-83)	Male 47 Female 11	60%
		Terbinafine solution vehicle as above	Entered 49 ITT 38	43 (25-72)	Male 18 Female 10	82%
Study 309	Multicenter, double-blind, double-dummy, randomized (1:1) clotrimazole-controlled	Terbinafine 1% solution twice daily for 7 days; vehicle 3 wk; 4 wk follow-up	Entered 348 ITT 311	47 (13-84)	Male 150 Female 67	98%
		Clotrimazole XXX twice daily for 4 wk; 4 wk follow-up	Entered 351 ITT 323	45 (12-85)	Male 147 Female 65	97%

Study Results

Whether applied once or twice daily for one week or once daily for two weeks, LAMISIL 1% topical solution was significantly more effective than placebo in the treatment of Tinea pedis but was comparable to cotrimazole.

Number (%) subjects with effective treatment (ET) or with both negative microscopy and culture (NM) at end of study

Study No.	Treatment	Treatment regimen	Results	
			ET	NM
SFF 351	LAMISIL Placebo	1 week, b.i.d.	66% 4% p<0.001	88% 14% p<0.001
SFF 301	LAMISIL Placebo	1 week o.d.	76% 21% p<0.001	85% 23% p<0.001
SFF 309	LAMISIL Cotrimazole	1 week, b.i.d.	83% 82% p=0.649	92% 91% p=0.411

Tinea versicolor

Study demographics and trial design

Summary of patient demographics for terbinafine 1% spray clinical trials in tinea versicolor

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
SFF 305	Randomized, multicenter, double-blind, vehicle-controlled (2:1 terbinafine:vehicle)	Terbinafine 1% solution twice daily for 7 days; 7 wk follow-up	Entered 79 ITT 76	34 (16-68)	Male 39 Female 37	89%
		Terbinafine solution vehicle twice daily for 7 days; 7 wk follow-up	Entered 36 ITT 34	32 (15-72)	Male 20 Female 14	91%
SFF 353	Randomized, multicenter, double-blind, vehicle-controlled (2:1 terbinafine:vehicle)	Terbinafine 1% solution twice daily for 7 days; 7 wk follow-up	Entered 109 ITT 97	34 (14-67)	Male 47 Female 50	84%
		Terbinafine solution vehicle twice daily for 7 days; 7 wk follow-up	Entered 49 ITT 47	34 (14-59)	Male 26 Female 21	81%

Study Results

When compared to placebo treatment, a one week twice daily application of LAMISIL 1% solution spray was significantly more effective in the treatment of Pityriasis versicolor. Treatment was effective in 70% of LAMISIL treated patients compared to 32% patients who used placebo ($p<0.001$). At the end of the study there was also a significant difference between the numbers of patients with negative microscopy, who had received LAMISIL treatment (79%) compared to the placebo treated (44%) [$p<0.001$].

Number (%) subjects with effective treatment (ET – primary variable[1]) or negative microscopy (NM) at end of study

Study	Treatment	Number of patients (%)	
		ET	NM
SFF 305	LAMISIL Placebo	52 (70%) 11(32%) p<0.001	58 (79%) 15 (44%) p<0.001
SFF 353	LAMISIL Placebo	75 (77%) 13 (28%) p<0.001	76 (78%) 14 (30%) p<0.001

[1]Effective treatment is defined as negative microscopy and a total sign/symptom score of 0 or 1.

DETAILED PHARMACOLOGY

The mechanism of action of terbinafine involves specific inhibition of fungal ergosterol biosynthesis at the point of squalene epoxidation, leading to a deficiency of an essential component of the fungal cell membranes (i.e. ergosterol) and to intracellular accumulation of the precursor squalene. The latter effect appears to be responsible for the primary fungicidal activity, its consequent disruption of cell membranes and cell wall synthesis having been noted in ultrastructural studies of terbinafine treated fungi. This mechanism distinguishes terbinafine from the azole antimycotics, which affect a later step in ergosterol biosynthesis by inhibiting 14 %-demethylase, a cytochrome P-450 enzyme upon which terbinafine has no effect. In contrast to many azoles, terbinafine does not bind to cytochromes P-450 in mammalian steroidogenic tissues.

Oral

The pharmacokinetics of orally administered terbinafine in plasma can best be described by a 2-compartment model. More than 80% of the dose is absorbed, clearance of the drug is high, it is extensively metabolized in the liver, and it is extensively distributed in the tissues. The peak plasma concentration is proportional to the dose, and the time to peak is ~ 2 hours, independent of the dose.

Mean concentrations of terbinafine (in µg/g) measured in the stratum corneum, dermis/epidermis, hair, sweat, and sebum during and after 12 days of 250 mg LAMISIL per day in 10 healthy volunteers were as follows before (day 0), during (days 2, 6, 12) and after treatment (days 13 and 16).

Day	**0**	**2**	**6**	**12**	**13**	**16**
Stratum corneum	0.11	0.86	2.84	9.05	5.08	3.06
Derm / epiderm	0	0.05	0.23	0.35	0.11	0.14
Sebum	0	38.2	43.1	39.7	45.1	18.8
Hair	0.02	0.24	1.30	2.60	2.11	1.35
Sweat	0	0	0	0	0	0

The pattern of tissue distribution suggests a rapid diffusion of drug through the dermis/lower epidermis into the stratum corneum, where maximal concentrations were achieved at day 12, and the $t_{1/2}$ was 3-4 days (this implies that the concentrations of terbinafine would remain above the MIC for most dermatophytes for 3 weeks). Another route of terbinafine distribution likely to be important for the treatment of dermatomycosis would be secretion into sebum, in which drug levels were high and persisted for several days after cessation of treatment.

In a study evaluating the efficacy of terbinafine in the treatment of onychomycosis, plasma levels were measured monthly in 9 patients, half of whom received 250 mg terbinafine q.d. in the evening and the other half 125 mg b.i.d. A pharmacokinetic steady state was attained at or before 4 weeks, the first analysis time point available. The steady-state plasma concentrations were 0.22 - 0.56 and 0.15 - 0.35 µg/ml for the b.i.d. and q.d. doses, respectively, and did not increase over time.

Topical

Pharmacokinetic studies in humans revealed that absorption of terbinafine cream or spray through skin is less than 5%. In a single dose study of ^{14}C-terbinafine, urinary excretion accounted for ~ 90% of the absorbed dose, and the highest concentration appeared in the urine 2 and 3 days after terbinafine application.

Microbiology

In vitro

The minimum inhibitory concentrations (MICs) of terbinafine were determined by serial dilution tests against yeasts, molds, dermatophytes, the mycelial form of Candida albicans, Pityrosporum spp., and Sporothrix schenkil. The spectrum and MIC values obtained for the various species and strains of fungi at different research laboratories (summarized as a range of activity in the following table) demonstrate that terbinafine possesses a high activity against dermatophytes, aspergilli, and dimorphous or dermatiaceous fungi. The susceptibility of blastospores of various species and strains of yeasts to terbinafine is much lower with MIC's ranging from 0.1 to > 128 µg/ml. The efficacy of terbinafine against 2 clinically important yeasts was confirmed by an evaluation of the susceptibility of 78 clinical isolates of Candida albicans and 20 of Candida parapsilosis. Blastophores of the Candida parapsilosis were more sensitive than those of Candida albicans, but the mycelial growth form of the Candida albicans (considered the pathogenic form) was the most sensitive form (MIC 50 = 0.195 µg/mL).

Summary of results published on *in vitro* activities of terbinafine against pathogenic and opportunistic fungi

Fungus	MIC range (µg/mL)
I. Dermatophytic Fungi	
Trichophyton mentagrophytes	0.001-0.01
rubrum	0.001- 0.01
rubrum verrucosum	0.001- 0.006
Epidermophyton floccosum	0.001-<0.06
Microsporum canis	0.005-0.01
Microsporum gypseum	0.005-0.01
Microsporum persicolor	0.002-0.003

II.	**Filamentous Fungi**	
	Aspergillus spp.	0.005-5.0
	Aspergillus flavus	0.01-0.5
	Aspergillus fumigatus	0.02-5.0
	Aspergillus niger	0.005-0.5
	Aspergillus terreus	0.05-5.0
	Pseudallescheria boydii	32.00->64.0
	Mucor, Rhizopus spp.	64.0->128.00
	Acremonium spp.	1.0-4.0
	Curcularia fallax	0.25-0.5
	Fusarium spp.	32.0->64.0
	Hendersonula toruloidea	1.0-4.0
	Lasiodiplodia theobromae	0.25-0.5
	Paecilomycea spp.	8.0-64.0
	Scopulariopsis brevicaulis	0.5-8.8
	Scytalidium hyalinum	1.0-4.0
III.	**Dimorphic Fungi**	
	Blastomyces dermatitidis	0.05-0.39
	Histoplasma capsulatum	0.05-0.2
	Sporothrix schenckii	0.05-2.0
IV.	**Pathogenic Yeasts**	
	Candida albicans (yeast form)	6.25->128.0
	Candida albicans (mycelial form)	0.098-0.78
	Candida parapsilosis	0.1-3.13
	Candida tropicalis	10.0-128.0
	Candida pseudotropicalis	0.5-50.0
	Candida krusei	50.0->100.0
	Candida guilliermondii	6.25-100.0
	Candida glabrata (T.glabrata)	>100.0->128.0
	Cryptococcus neoformans	0.25-2.0
	Pityrosporum spp.	0.2-0.8
V.	**Dematiacese**	
	Phaechyphomycosis complex*	<0.06- 0.5
	Chromoblastomycosis complex**	0.06-2.0

* = *Exophiala jeanselmei, Wangiella dermatitidies, Cladosporium bantianum*
** = *Fonseceas pedrosoi, Phialophora spp.*

Terbinafine was primarily fungicidal against T. mantagrophytes, M. canis, A. fumigatus, Sc. brevicaulis, S. schenkii, and C. parapsilosis, and fungistatic against C. albicans.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD50
Mouse	M,F	Oral	>4 g/kg
	M,F	i.v.	393 mg/kg
	M,F	1% solution orally	> 250 mg/kg
Rat	M,F	Oral	>4 g/kg
	M,F	i.v.	213 mg/kg
	M,F	1% cream orally	25 mg/kg (no mortalities)
	M,F	1% solution orally	>200 mg/kg
Rabbits	M,F	Topical (suspension)	>1.5 g/kg

Long Term Toxicity

LONG-TERM TOXICITY

SPECIES	LENGTH OF ADMIN.	ROUTE	DOSES (mg/kg)	RESULTS
RAT	26 weeks	oral	0, 30, 100, & 300	↑ in liver weights in the mid & high dose groups; ↑ in kidney and heart weights in high dose group; ↑adrenal weight all dose groups. In all animals allowed a recovery period organ weights showed signs of reversibility. At all doses males showed ↑ incidence & severity of spontaneous nephropathy. At mid & high doses, livers of female rats showed enlargement of centrilobular hepatocytes. Histological evidence of recovery in liver but not in kidney on cessation of treatment.
	52 weeks	oral	M: 6.9, 20, 68 F: 9.3, 28, 95	Reversible ↑ in kidney weight in mid and high-dose males and liver weight in high dose females. No histopathological organ or tissue changes or evidence of drug-related tumorigenesis. No proliferation of smooth endoplasmic reticulum or peroxisomes. No-toxic-effect level in males 68 mg/kg; in females 95 mg/kg.
Pre and Post pubertal RATS	55 days	oral	0, 25, 75, 250	In 15 day old rats treated until 70 days of age, the mid and high doses were toxic as shown by death of some animals at these dose levels. Reduction in mean body weight gain was also seen in these dose groups.
Juvenile RATS	55 days	oral	0, 10, 25, 45, 100	Well tolerated in rats treated from 15 to 70 days of age. 1 death in low dose group. Slight increase in liver weights of high dose females.
DOGS	26 weeks	oral	0, 20, 60, 200	Initial hypersalivation in mid and high dose groups; sporadic emesis in high dose group. Haematological parameters remained unchanged throughout experiment. At end of treatment livers of 3 of 4 high dose dogs contained lamellated intracytoplasmic inclusions. The no-toxic-effect level was 60 mg/kg.
	52 weeks	oral	0, 10, 25, 100	Mid and high dose groups showed sporadic emesis and slightly inhibited body weight gain. High dose groups showed sporadic hypersalivation and reduced food intake. Females of all dose groups showed slightly lower triglyceride values.
RABBITS	4 weeks	topical (2%cream)	10, 20, 40	Moderate reactions (erythema) at the application site.
	4 weeks	topical (1% solution)	0, 5, 15, 30	Skin site showed erythema, edema and papules in all groups including placebo controls.
	26 weeks	topical (1% & 2%cream)	10, 20, 40	Slight erythema and edema in all groups including placebo controls.

REPRODUCTION STUDIES

SPECIES	DURATION	ROUTE OF ADMIN.	DOSES (mg/kg)	RESULTS
RATS	Fertility & Reproduction Study M: 63 days prior to mating F: 14 days prior to mating to weaning	oral	10, 50, 250	In the high dose group a lower pregnancy rate, mean number of implants and living pups per dam were observed as well as a high pre- and perinatal offspring mortality. Physical and functional development of the offspring was also retarded. The fertility and general reproductive performance of the offspring were normal at all dose levels tested.
	Embryotoxicity study Days 6 to 15 postcoitum	oral	30, 100, 300	Inseminated female rats treated with terbinafine tolerated doses up to 100 mg/kg well. Lower body weight gain was seen at 300 mg/kg. No embryolethal or teratogenic effects were seen.
	Peri & post-natal study Day 15 postcoitum to day 21 postpartum	oral	30, 100, 300	Inseminated female rats treated with terbinafine tolerated all doses well. No clinical signs or relevant reproductive changes in any group.
	Embryotoxicity study Day 6 to 15 postcoitum	subcutaneous	10, 30, 100	In the high dose group dams gained less body weight and had skin irritation at the injection site. A tendency to lower body weight gains was also noted in the mid-dose group. No adverse effects observed on pregnancy or embryonic or fetal development in any group.
RABBITS	Embryotoxicity study Day 6 to 18 postcoitum	oral	30, 100, 300	Inseminated female rabbits treated with terbinafine tolerated doses up to 100 mg/kg well. In the high-dose group weight loss was observed in some dams, 2 of which had to be euthanized due to poor health. No relevant reproductive alterations were seen at any dose level.

Mutagenicity

In vitro and *in vivo* mutagenicity testing revealed no specific mutagenic or genotoxic properties of terbinafine. *In vitro* tests of cell transformation to malignancy were negative.

CARCINOGENICITY

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MICE	100 weeks	oral	M: 14, 40, 130 F: 16, 60, 156	There was a slight inhibition of body weight gain in the mid- and high-dose females. Macroscopic and microscopic examinations revealed no neoplastic or other findings which were attributable to treatment with terbinafine.
RATS	123 weeks	oral	M: 6.9, 20, 69 F: 9.6, 28, 97	Ophthalmoscopy revealed an ↑ in incidence of cataracts in males at high doses. No treatment related cataract changes occurred after 52 weeks, and such eye changes are known to occur spontaneously in old rats. ↑ incidence of enlarged swollen livers and liver nodules in the high dose animals, particularly males. Slight ↑ incidence of hepatocellular tumours in the high dose males. Females of the high dose group showed a slightly greater incidence and extent of hepatocellular necrosis, suggesting the high dose was at the threshold of a toxic response.

Additional studies

The following additional chronic toxicity and genotoxicity studies were performed to investigate the findings of the life-time rat study and their relevance to man.

4-week oral toxicity study in rats with special emphasis on hepatic alterations

4-WEEK ORAL TOXICITY STUDY IN RATS WITH SPECIAL EMPHASIS ON HEPATIC ALTERATIONS

SPECIES	DURATION	ROUTE	DOSES (mg/kg)
RAT	4 weeks	oral	M: 100, 465; F: 108, 530
RESULTS			
FEED INTAKE & BODY WEIGHT GAIN	Only at the high dose level were significant decreases in food intake and body weight gain recorded.		
CLINICAL CHEMISTRY	At the high-dose level reduced serum glucose (both sexes) and serum triglyceride levels (both sexes) and increased SGPT, SAP (females), and BUN (males) were seen. Significantly lower corticosterone plasma levels were found in high-dose animals and higher testosterone and estradiol plasma levels in low-dose males and females respectively.		
LIVER MEASUREMENTS	Increased cytochrome P-450 content (high dose males) cytochrome b_5 contents (high dose males and females), cytochrome b_5 reductase activity (high dose males), 7-ethoxy-coumarin-O-deethylase activity (per mg cytochrome P-450; in low- and high-dose females), and peroxisomal palmitoyl-CoA epoxidase activity (low dose females and high dose males and females). Determination of liver compartments indicated a slight reduction of water content (high dose males), an unchanged protein content, and an increased lipid moiety (low dose males and high-dose males and females).		
POSTMORTEM FINDINGS	Increased absolute and relative liver, and relative kidney weights (high dose males and females), mild hepatic centrilobular hypertrophy (high-dose only), increase in peroxisome numbers, and abnormal peroxisome shape (high-dose males). Slight increase in hepatic peroxisome size and number (high dose males and females). In high-dose group, numerous abnormal peroxisomes were found in both sexes, as well as a slight proliferation of the SER.		

Effects of 13-week treatment on selected toxicological variables in rats

EFFECTS OF A 13-WEEK TREATMENT ON SELECTED TOXICOLOGICAL VARIABLES IN RATS

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
RATS	13 weeks	oral	M: 72 F: 102	Slight decrease in serum triglycerides (significant in males only), slight increase in albumin (females); these changes were observed in test weeks 5 and 8 only. Relative liver weights were increased as was palmitoyl-CoA epoxidase activity. There was no evidence of hepatic peroxisomal morphological abnormalities; however peroxisome numbers were increased in both sexes.

4-week oral toxicity study in mice

4-WEEK ORAL TOXICITY STUDY IN MICE

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MICE	4 weeks	oral	M: 103, 510 F: 107, 512	Slightly impaired liver function in males only. Slight induction of the cytochrome P-450 and b_5 systems was seen (biologically relevant only at the high-dose level and more marked in males than females), as well as ethoxycoumarin-O-deethylase activity. The peroxisomal marker palmitoyl-CoA-epoxidase was slightly increased at all dose levels (in both sexes); no changes in the size or number of perosixomes were seen. There seemed to be a link between the degree of induction of some major hepatic enzyme systems and the moderate hepatic centrilobular hypertrophy observed histologically (and more generally the liver weight increases). Endocrinological examinations revealed higher basal corticosterone levels in a number of low and high-dose animals.

Preliminary toxicity study in monkeys

PRELIMINARY TOXICITY STUDY IN MONKEYS

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MONKEYS	28 days	by gavage	500	Emesis and hypersalivation were observed on several occasions. The female showed consistent weight loss during the first 3 weeks and slight recovery thereafter. Liver weights were increased in both the treated animals, but there were no histopathological changes. No treatment-related changes in the peroxisome population or general cellular ultrastructure were seen. Increased activity of hepatic palmitoyl CoA-epoxidase indicated increased peroxisomal fatty oxidation. Cytosolic epoxide hydrolase activity was below detectable limit.

32-week oral toxicity in monkeys

32-WEEK ORAL TOXICITY STUDY IN MONKEYS

SPECIES	DURATION	ROUTE	DOSE (mg/kg)	RESULTS
MONKEY	32 weeks	Oral	50, 150, 300	Eye lesions were seen after 26 weeks of treatment. Ophthalmoscopy revealed white spots on the retina in mid and high dose animals. No similar changes were seen at earlier examination. No morphological changes were seen in any layer of the retina. After withdrawal of terbinafine, the changes described recover fully (after a 13 week recovery period).

Test for tumour-initiating activity in the rat liver foci bioassay

After partial hepatectomy, rats were treated with a single oral dose of 1 g/kg terbinafine (controls were treated with N-nitrosomorpholine [NNM]) followed by an 8-week treatment with phenobarbital (for promotion of growth of putative preneoplastic foci). A significant increase in foci/cm was seen only in NNM-treated animals in comparison with the respective control groups. No differences were observed between control animals (treated only with phenobarbital) and those treated with terbinafine plus phenobarbital. It was concluded that terbinafine did not have tumour-initiating potential even in combination with a tumour promoting agent.

Autoradiographic determination of the induction of DNA repair/synthesis and cell replication in rat hepatocyte primary cultures after *in vivo* treatment

No evidence was found for any induction of either DNA repair or DNA replication in the hepatocytes from terbinafine treated rats, and the frequency of replicating nuclei were in the control range.

Mutagenicity test using Salmonella typhimurium

Liver fractions from male rats treated for 13 weeks with 69 mg/kg/day of terbinafine and non-treated control rats were used to evaluate terbinafine for genetic activity. There was no evidence that repeated treatment of rats with terbinafine induces enzymes capable of producing mutagenic intermediates of terbinafine.

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PART III: CONSUMER INFORMATION

PrLAMISIL®

Terbinafine tablets 250 mg (as terbinafine hydrochloride)

Terbinafine hydrochloride topical cream 1% w/w (10 mg/g)

Terbinafine hydrochloride topical spray solution 1% w/w (10 mg/g)

This leaflet is part III of a three-part "Product Monograph" published when LAMISIL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LAMISIL. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet. You may need to read it again. This medicine has been prescribed only for you. Do not give it to anybody else or use it for other illnesses. Read all of this leaflet carefully before you start treatment. Follow all your doctor's instructions carefully, even if they differ from the general information contained in this leaflet.

ABOUT THIS MEDICATION

What the medication is used for:

LAMISIL is used to treat fungal infections of skin, fingernails and toenails:

- LAMISIL tablets are used to treat fungal infections of the nail (toes, fingers) and may be used for certain fungal skin infections that do not respond to topical treatment.
- LAMISIL cream and spray are used to treat certain fungal skin infections of the skin.

Consult your doctor to confirm which type of fungal skin infection you have. Your doctor can determine if LAMISIL is the right treatment for you.

The treatment should only be taken as prescribed by your doctor. Some evidence of infection may still be present at the end of treatment. This will gradually diminish.

What it does

Terbinafine interferes in the production of a substance (ergosterol) that the fungus needs to grow and causes a build-up of another substance in the cells (squalene). Both actions cause the death of the fungus and elimination of the infection.

When it should not be used:

Do not use LAMISIL if you are allergic to terbinafine (the active antifungal ingredient) or any of the ingredients in the formulation (See *What the nonmedicinal ingredients are*). If you think you may be allergic, ask your doctor for advice.

Do not use LAMISIL if you have chronic or active liver disease.

Important information about some of the ingredients

If any of these apply to you, tell your doctor before you take LAMISIL.

LAMISIL Cream contains benzyl alcohol, cetyl alcohol and stearyl alcohol which may cause local skin reactions (e.g contact dermatitis).

LAMISIL Spray contains propylene glycol and ethanol which may cause skin irritation.

What the medicinal ingredient is:

terbinafine hydrochloride

What the non-medicinal ingredients are:

Tablets: cellulose microcrystalline; magnesium stearate; methylhydroxypropylcellulose; silica, colloidal anhydrous; sodium carboxymethyl starch.

Cream: benzyl alcohol; cetyl alcohol; cetyl palmitate; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; stearyl alcohol.

Spray: cetomacrogol 1000; ethanol (28.8% v/v); propylene glycol; water.

What dosage forms it comes in:

Oral: 250 mg Tablets
Topical: 1% topical cream 10 mg/g
1% topical spray solution 10 mg/g

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LAMISIL (terbinafine hydrochloride) tablets must not be used if you have pre-existing chronic or active liver disease. Serious and life-threatening cases of liver failure, including death, or requiring liver transplant, have been reported in patients with or without pre-existing chronic or active liver disease receiving LAMISIL Tablets.

Stop taking LAMISIL tablets and consult your doctor immediately should you develop jaundice (yellowness of skin and/or eyes or other symptoms). See *Table of Serious Side Effects*.

Your doctor may order blood tests before you start LAMISIL and during LAMISIL treatment.

Before you use LAMISIL, talk to your doctor if you:

- have or have a history of any other medical problems such as liver or kidney problems, blood diseases (e.g. anemia), serious skin reactions, or alcohol abuse
- if you have or have had liver problems, your doctor may require blood tests before and during LAMISIL treatment to test liver function
- are allergic to any other medicines (either prescription or non-prescription) or foods
- are pregnant or intend to become pregnant while using LAMISIL.
- are breast-feeding; oral LAMISIL is excreted in breast milk. Nursing mothers should avoid topical applications of LAMISIL to the breast and infants

should not come into contact with areas treated with topical LAMISIL.

Contact your doctor immediately, while taking LAMISIL, if you develop conditions such as:

- liver problems with symptoms such as persistent nausea, vomiting, abdominal pain, dark urine, pale stools, fatigue, loss of appetite, yellowing of the skin and eyes
- serious skin reactions such as blistering or peeling skin, blistering of the lips, eye or mouth, red/inflamed skin, hives, fever (due to skin reactions), rash (due to high white blood cell count-eosinophilia)
- experience symptoms of lupus erythematosus such as thickened patches of red/silver skin (psoriasis) , joint pain, muscle disorder/pain and fever
- blood disorder with symptoms such as weakness, unusual bleeding, bruising, sore throat or frequent infections

INTERACTIONS WITH THIS MEDICATION

Tablets:

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including herbal medicines, oral contraceptives (birth control pills) and non-prescription medicines. Some other medicines may interact with LAMISIL. These include:

- some medicines used to treat infectious diseases called antibiotics (e.g. rifampicin),
- some medicines used to treat mood disorders (some antidepressants (such as tricyclic antidepressants, selective serotonine reuptake inhibitors including class 1A, 1B and 1C, monoamine oxidase inhibitors Type B, desipramine),
- some medicines used to treat irregular heart rhythm (antiarrhythmics (e.g. propafenone, amiodarone),
- some medicines used to treat high blood pressure (e.g. beta-blockers such as metoprolol),
- theophylline, a medicine used to relieve bronchospasm in asthma
- some medicines used to treat cough (e.g. dextromethorphan),
- cyclosporine, a medicine used to control your body's immune system (e.g. in order to prevent rejection of transplanted organs).
- St John's wort [*Hypericum perforatum]),* a herbal medicine used to treat depression

Some cases of menstrual irregularities and pregnancies have been reported in patients taking LAMISIL concomitantly with oral contraceptives; however, the rate of occurrence appears to be within the background incidence for patients taking oral contraceptives alone.

Cream and spray:

No drug interactions are known to date.

PROPER USE OF THIS MEDICATION

To help clear up your infection completely, it is very important that you keep taking this medicine for the prescribed treatment period, even if your symptoms begin to clear up or you begin to feel better after a few days. Since fungal infections may be very slow to clear up, stopping your medication too soon can cause the symptoms and the fungal infection to flare up again.

Missed Dose:

Try not to miss any doses. If you do miss a dose, take it as soon as possible. However, if it is almost time for your next dose (up to 4 hours), skip the missed dose and go back to your regular schedule. Do not double the doses and never make dose changes on your own. Take as prescribed by your doctor.

Usual Adult Dose

Follow your doctor's instructions carefully. Do not exceed the recommended dosage. If you have the impression that the effect of LAMISIL is too strong or too weak, talk to your doctor or pharmacist.

ORAL

LAMISIL tablets

Adults: 250 mg once daily.

Taking LAMISIL at the same time each day will help you remember when to take your medicine. LAMISIL tablets can be taken on an empty stomach or after a meal.

You can take LAMISIL tablets if you are aged 65 years and over at the same dose as younger adults.

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

TABLE I

Indication	Duration of Treatment
Onychomycosis (of fingers and toes)	6 weeks to 3 months
Skin Infections Tinea pedis (interdigital & plantar/moccasin type)	2-6 weeks
Tinea corporis, cruris	2-4 weeks

TOPICAL

If the cream accidentally gets into your eyes, wipe it away and rinse the eye thoroughly with running water. Consult your doctor if symptoms persist.

Avoid applying the spray to your face.

LAMISIL Cream and Spray contain alcohol (ethanol) which could be irritating to certain skin lesions.

Because tinea and yeast infections can be passed to other people, remember to keep your own towel and do not share them with others. To protect yourself from re-infection, your towels and clothes should be washed frequently.

LAMISIL cream

LAMISIL cream can be applied once or twice daily.

The affected areas should be cleansed and dried thoroughly before application of LAMISIL.

The cream should be applied to the affected skin and surrounding area in a thin layer and rubbed in lightly.

In the case of skin-fold infections (under breasts, between toes, around the groin, between the buttocks) the application may be covered with a gauze strip, especially at night.

The duration of treatment varies with the indication and is dependent on the severity of the infection:

TABLE II

Indication	Duration of Treatment
Tinea pedis	1 week, once a day
Tinea corporis/cruris	1 week, once a day
Cutaneous Candidiasis	1 to 2 weeks, once or twice a day
Pityriasis versicolor	2 weeks, once or twice a day

If there are no signs of improvement after two weeks you should talk to your doctor.

LAMISIL spray

LAMISIL spray is applied once or twice daily, depending on the indication.

The affected areas should be cleansed and dried thoroughly before application of LAMISIL. Avoid contact with cuts, wounds or other skin lesions as the alcohol in the spray may irritate or sting the skin.

A sufficient amount of solution should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area.

In case of accidental inhalation, contact your doctor if any symptoms develop and persist.

The duration of treatment varies with the indication and is dependent on the severity of the infection:

TABLE III

Indication	Duration of Treatment
Tinea pedis	1 week once a day
Tinea corporis/cruris	1 week once a day
Pityriasis versicolor	1 week twice a day

Relief of clinical symptoms usually occurs within a few days. Irregular use or premature discontinuation of treatment carries the risk of recurrence. If there are no signs of improvement after two weeks you should talk to your doctor.

There are other measures that you can take to help clear up your infection and make sure it does not return. For example, keep the infected areas dry and cool and change clothing that is in direct contact with the infected area(s) daily.

Overdose:

Symptoms caused by an overdose of LAMISIL tablets include headache, nausea, stomach pain and dizziness.

No case of overdosage has been reported with LAMISIL cream or spray. Should, however, LAMISIL cream, or spray, be inadvertently ingested, adverse effects similar to those observed with an overdosage of LAMISIL tablets are to be expected. The alcohol content of the spray (28.8% v/v) has to be taken into account. Ask your doctor if you do not understand these instructions or want more information.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

LAMISIL tablets

As with all medicines, some patients taking LAMISIL tablets may experience some unwanted effects (side effects), although not everybody gets them.

The following side effects have been reported with LAMISIL tablets:

Very common (*likely to affect more that 1 in every 10 patients*): headache, nausea, mild abdominal pain, stomach discomfort after meal (heartburn), diarrhea, swelling or bloating (a feeling of fullness) of the abdomen, loss of appetite, skin rashes (itchy), joint pain and muscle pain.

Common (*likely to affect 1 to 10 in every 100 patients*): Mood disorder (depression), disturbance or loss of sense of taste, dizziness, eye disorder and tiredness. If you suffer dizziness, do not drive or operate machinery.

Uncommon (*likely to affect 1 to 10 in every 1,000 patients*): If you notice abnormal pale skin, mucosal lining or nail beds, unusual tiredness or weakness or breathlessness on exertion (possible signs of a disease that affects the level of red blood cells), anxiety, tingling or numbness and decreased skin sensitivity, increased sensitivity of the skin to sun, noises (e.g. hissing) in ears, fever and weight loss.

Rare *(likely to affect less than 1 to 10 in every 10,000 patients)*: Yellow eyes or skin (liver problems) and abnormal liver function test results.

Very rare (*likely to affect less than 1 in every 10,000 patients*): Decrease in certain types of blood cells, lupus (an autoimmune disease), serious skin reactions, allergic reactions, psoriasis-like skin eruptions (rash with silver coloured appearance), worsening of psoriasis, skin rash with flaking or peeling and hair loss.

If you experience smell, taste, visual or hearing disorders or symptoms of depression, then stop using LAMISIL and call your doctor.

If any of the listed side effects affect you severely, discuss this with your doctor.

Other side effects not listed above may also occur in some patients. If you notice any other side effects not mentioned in this leaflet, inform your doctor or pharmacist.

Some side effects could be serious:

- if you develop fever, shivering, a sore throat or mouth ulcers due to infections and weakness or if you get infections more frequently or
- if you experience difficulty in breathing, dizziness, swelling mainly of the face and throat, flushing, crampy abdominal pain and loss of consciousness or if you experience symptoms such as joint pain, stiffness, rash, fever or swollen/enlarged lymph nodes (possible signs of severe allergic reactions).
- If you develop any skin problems such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever.
- If you experience severe upper stomach pain with radiation to the back (possible signs of pancreas inflammation).
- If you experience unexplained muscle weakness and pain or dark (red-brown) urine (possible signs of muscle necrosis).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Liver problems, sometimes fatal with symptoms such as persistent nausea and vomiting, abdominal pain, fatigue, loss of appetite, dark urine, pale stools or jaundice (yellowing of the skin and eyes).			√
Very rare	Blood abnormalities with symptoms of sore throat, fever, mouth sore, unusual bleeding or bruising,			√
	Inflammation of the blood vessels (vasculitis) or the pancreas (pancreatitis)			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your
	Serious allergic reactions (anaphylactic or serum sickness reactions) or infections			√
	Muscle breakdown (rhabdomyolysis)			√
	Immune system disorders (lupus)			√
	Serious skin reactions (blistering, peeling skin)			√

LAMISIL cream and spray

The following side effects have been reported with LAMISIL cream and spray; however, treatment rarely has to be discontinued for this reason.

Common (*likely to affect 1 to 10 in every 100 patients*):

Flaking or peeling of the skin (skin exfoliation), itching (pruritus).

Uncommon (*likely to affect 1 to 10 in every 1,000 patients*):

Skin lesion, scab, skin disorder, change in the color of the skin (pigmentation disorder), redness of the skin (erythema), skin burning sensation, pain, application site pain, application site irritation.

TELL your doctor if you notice any of these possible side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown	Allergic reaction (hypersensitivity)	√		

HOW TO STORE IT

Store at temperatures between 15°C and 30°C.

Protect tablets from light.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.Novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883

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