PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr LAMISIL®

Terbinafine Hydrochloride

Tablets, 250 mg, oral

Cream, 1% w/w (10 mg/g), topical

Spray solution, 1% w/w (10 mg/g), topical

Antifungal

ATC code: D01AE15

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RECENT MAJOR LABEL CHANGES

None at the time of authorization

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LAMISIL® (terbinafine hydrochloride) is indicated for:

- 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*.

LAMISIL tablets:

- 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.
- 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: LAMISIL tablets are not effective in pityriasis versicolor (also known as *Tinea versicolor*).

LAMISIL cream and spray:

- ***Cream***
    - 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*).
    - the treatment of pityriasis (tinea) versicolor due to Malassezia furfur.
- ***Spray***
    - the treatment of fungal infections of the skin caused by dermatophytes such as trichophyton.
    - the treatment of pityriasis (tinea) versicolor due to Malassezia furfur.

Note: LAMISIL cream and spray are not effective in onychomycosis.

1.1 Pediatrics

Pediatrics (< 18 years of age): *No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use*.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. (See 7.1.4 Geriatrics)

2 CONTRAINDICATIONS

- LAMISIL tablets and LAMISIL cream and spray are contraindicated in patients with a known hypersensitivity to terbinafine or to any of the excipients of LAMISIL or component of the container. See 6 DOSAGE FORMS, STRENGTHS, and COMPOSITION AND PACKAGING.
- Lamisil tablets are contraindicated for patients with chronic or active hepatic disease. See 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

- **HEPATIC:** LAMISIL 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 and should be discontinued if biochemical or clinical evidence of liver injury develops. See 7 WARNINGS AND PRECAUTIONS, Hepatic.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Special Populations

- **Liver Impairment:** LAMISIL tablets are contraindicated for patients with chronic or active hepatic disease. See 2 CONTRAINDICATIONS and 7 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.

4.2 Recommended Dose and Dosage Adjustment

- ***LAMISIL tablets:***
    - Adults: 250 mg once daily. See 4.1 Dosing Considerations.

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

Table 1

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.

- ***LAMISIL cream:***
  - LAMISIL cream can be applied once or twice daily depending on the indication.
  - The duration and frequency of treatment varies with the indication and is dependent on the severity of the infection:

Table 2

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

    Table 3

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.

4.4 Administration

Tablets: 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.

Cream: 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.

Spray: The affected areas should be cleansed and dried thoroughly before application of LAMISIL. A sufficient amount of spray should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area. See 7 WARNINGS AND PRECAUTIONS.

4.5 Missed Dose

If a dose of LAMISIL tablets is missed, the patient should be advised to take it as soon as he/she remembers. However, if it is almost time of the next dose (up to 4 hours), the patient should skip the missed dose and go back to the regular dosing schedule. The patient should not double dose.

5 OVERDOSAGE

LAMISIL Tablets

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.

LAMISIL cream and spray

No case of overdosage has been reported. The low systemic absorption of LAMISIL cream and spray 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 tablets. However, should, larger amounts of LAMISIL cream and spray 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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
oral	Tablet 250 mg	cellulose microcrystalline granulate; hypromellose; magnesium stearate; silica, colloidal anhydrous; sodium starch glycollate.
topical	Cream, 1 % w/w (10 mg/g)	benzyl alcohol; cetyl alcohol; cetyl palmitate; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; stearyl alcohol.
topical	Spray, 1 % w/w (10 mg/g)	ceto-macrogol 1000; ethanol (28.8% v/v); propylene glycol; water.

LAMISIL 250 mg tablets are whitish to yellow tinged white, circular, biconvex, with bevelled edges tablet, scored on one side and embossed "LAMISIL 250". Available in bottles of 100 and 500 tablets and blister packs of 28 tablets (14 tablets per blister).

LAMISIL cream 1 % is white, smooth or almost smooth, glossy cream with a weak characteristic odor. Available in 15 or 30 gram tubes.

LAMISIL spray 1 % is Colourless to faintly yellow clear liquid. Available in 30 mL bottles.

7 WARNINGS AND PRECAUTIONS

LAMISIL Tablets

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

Driving and Operating Machinery

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.

Endocrine and 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 9 DRUG INTERACTIONS.

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.

Hepatic/Biliary/Pancreatic

LAMISIL 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 tablets 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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 8 ADVERSE REACTIONS.

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.

Monitoring and Laboratory Tests

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

Neurologic

Sensory disturbances:

Disturbances of visual, auditory and tactile senses have been reported. See 8 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.

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.

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.

Renal

The pharmacokinetics of LAMISIL have been investigated in patients with renal impairment (creatinine clearance $\leq$ 50 mL/ min); based on this study the use of LAMISIL in renally impaired patients is not recommended. See 10.3 Pharmacokinetics.

Reproductive Health: Female and Male Potential

Please see 7.1.1. Special Population

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.

- **Fertility:** No effect of terbinafine on fertility has been seen in animal studies (see section 16 NON-CLINICAL TOXICOLOGY) and there are no data to suggest an effect on fertility in humans.

Skin

LAMISIL tablets

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.

LAMISIL cream and spray

LAMISIL cream and spray are for external use only. LAMISIL cream and spray 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 contains propylene glycol which may cause skin irritation.

7.1 Special Populations

7.1.1 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, LAMISIL tablets or LAMISIL cream should not be used during pregnancy.

7.1.2 Breast-feeding

Terbinafine is excreted in breast milk; therefore mothers receiving LAMISIL tablets 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 cream and spray to the breast. In addition, infants must not come into contact with any treated skin area, including the breasts.

7.1.3 Pediatrics

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

LAMISIL should be kept out of the reach of children.

7.1.4 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 LAMISIL tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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).

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 5 Clinical Trial Adverse events

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

8.3 Less Common Clinical Trial Adverse Reactions

Adverse events not frequently observed (<1%) 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 7 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.

8.5 Post-Market Adverse 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.

9 DRUG INTERACTIONS

9.2 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 10.3 Pharmacokinetics).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Effects of other medicinal products on terbinafine:
The following medicinal products may increase the effect or plasma concentration of terbinafine.

Table 6-A Established or Potential Drug-Drug Interactions

Proper/common name	Source of Evidence	Effect	Clinical comment
Cimetidine	CT	Decreased the clearance of terbinafine by 33%	
Fluconazole	CT	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	CT	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	T	May increase the systemic exposure to terbinafine, based on predicted inhibition of CYP2C9 and CYP3A4 (no studies were performed)	
Amiodarone	T	May increase the systemic exposure to terbinafine, based on predicted inhibition of CYP2C9 and CYP3A4 (no studies	

Proper/common name	Source of Evidence	Effect	Clinical comment
		were performed).	
Cotrimoxazole (trimethoprim sulfamethoxazole)	CT	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	CT	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.	
Rifampicin	CT	May decrease the effect or plasma concentration of terbinafine (increased the clearance of terbinafine by 100 %)	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Effect of terbinafine on other medicinal products:

Table 6-B Established or Potential Drug-Drug Interactions

Proper/common name	Source of Evidence	Effect	Clinical comment
Drugs that are metabolized via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives)	C, CT	According to the results from studies undertaken in vitro and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance except with exception of those drugs that are metabolized via the cytochrome P450 system metabolized through CYP2D6 (see below). 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.	
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)	T, CT	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	

Proper/common name	Source of Evidence	Effect	Clinical comment
		oxidase inhibitors (MAO-Is) Type B, particularly if they also have a narrow therapeutic window (see 7 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.	
Antipyrine or digoxin	CT	Terbinafine does not interfere with the clearance of antipyrine or digoxin.	
Desipramine	CT	Terbinafine decreased the clearance of desipramine by 82%.	
Dextromethorphan/dextrorphan	CT	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.	
Ciclosporin	CT	Terbinafine increased the	

Proper/common name	Source of Evidence	Effect	Clinical comment
		clearance of ciclosporin by 15%.	
Fluconazole	CT	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.	
Cotrimoxazole (trimethoprim sulfamethoxazole)	CT	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.	
Zidovudine	CT	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	

Proper/common name	Source of Evidence	Effect	Clinical comment
		zidovudine.	
Theophylline	CT	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.	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

LAMISIL cream and spray:
No drug interactions are known to date.

9.5 Drug-Food Interactions

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

9.6 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.

10 CLINICAL PHARMACOLOGY

10.1 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.

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.

10.2 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.

10.3 Pharmacokinetics

LAMISIL tablets:

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: LAMISIL tablets 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.

Elimination: Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days.

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).

TABLE 7

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.

LAMISIL cream and spray:

Less than 5% of the dose is absorbed after topical application to humans; systemic exposure is thus very slight. Pharmacokinetic studies in humans revealed that absorption of terbinafine cream or spray through skin is less than 5%. In a single dose study of 14C-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.

Special Populations and Conditions

- **Hepatic Insufficiency*:*** Following a single 250 mg dose in 12 hepatically impaired cirrhotic (alcoholic) patients, total clearance of terbinafine was reduced by about 40%.

- **Renal Insufficiency:** 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.

11 STORAGE, STABILITY AND DISPOSAL

Tablets: Store at temperature between 15 and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Protect tablets from light.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: INN, BAN, USAN: terbinafine

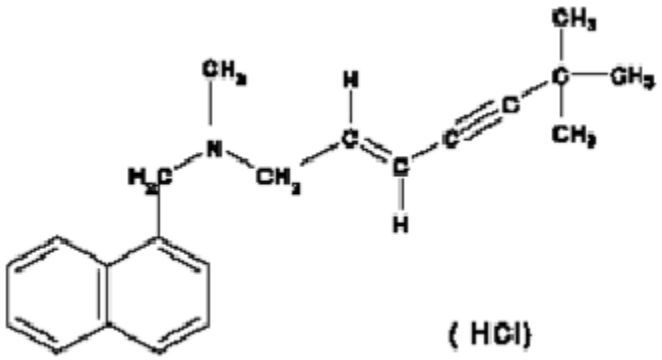
Chemical name: (E)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl-1-naphthaline-methanamine (-hydrochloride)

Molecular formula and molecular 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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Onychomycosis

LAMISIL tablets†

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

TABLE 8 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:

TABLE 9 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.

TABLE 10 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/Tinea cruris

LAMISIL tablets

Study demographics and trial design:

TABLE 11 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%
		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:

TABLE 12 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.

TABLE 13 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%)
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

TABLE 14 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

LAMISIL cream

Study demographics and trial design:

TABLE 15 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 Cream vehicle	Entered 78 Evaluable 66	31-39 (5-89)[1]	Male 27[1] Female 9[1]	Caucasian 51-67%
			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:

TABLE 16 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)

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)
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.

LAMISIL spray

Study demographics and trial design:

TABLE 17 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% spray 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,	Terbinafine 1% spray once daily for 7 days; 3 wk follow-up	Entered 32 ITT 26	41 (9-82)	Male 17 Female 9	81%

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
	multicenter	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% spray 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% spray was significantly more effective than placebo when applied once daily for one week in patients with Tinea corporis/cruris.

TABLE 18 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

LAMISIL tablets

Study demographics and trial design:

TABLE 19 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
		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:

TABLE 20 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.

TABLE 21 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.

LAMISIL cream

Study demographics and trial design:

TABLE 22 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:

TABLE 23 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.

TABLE 24 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)		

LAMISIL spray

Study demographics and trial design:

TABLE 25 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% spray 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% spray 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% spray 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% spray was significantly more effective than placebo in the treatment of Tinea pedis but was comparable to cotrimazole.

TABLE 26 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

Cutaneous Candidiasis

LAMISIL cream

Study demographics and trial design:

TABLE 27 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:

TABLE 28 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.

Tinea Versicolor

LAMISIL spray

Study demographics and trial design:

TABLE 29 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% spray 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%

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
SFF 353	Randomized, multicenter, double-blind, vehicle-controlled (2:1 terbinafine:vehicle)	Terbinafine 1% spray 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%) [$p<0.001$].

TABLE 30 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.

15 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).

TABLE 31 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.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

- Acute Toxicity:

TABLE 32 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:

TABLE 33 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.

TABLE 34 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.

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.

Genotoxicity: 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

TABLE 35 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

TABLE 36 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

TABLE 37 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

TABLE 38 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

TABLE 39 WEEK ORAL TOXICITY STUDY IN MONKEYS

SPECIES	DURATION	ROUTE	DOSE (mg/kg)	RESULTS
MONKEY	32 weeks	Oral	0, 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).

TABLE 40 Reproductive and Developmental Toxicology:

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.

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrLAMISIL®

Terbinafine Tablets

Terbinafine Hydrochloride topical cream

Terbinafine Hydrochloride topical spray solution

Read this carefully before you start taking **LAMISIL®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LAMISIL**.

Serious Warnings and Precautions

Do not take LAMISIL tablets 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 taking LAMISIL Tablets.

Stop taking LAMISIL tablets and consult your doctor immediately if you develop jaundice (yellowness of skin and/or eyes). See Table of Serious Side Effects and what to do about them.

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

What is LAMISIL 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 infections of the skin.

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.

How does LAMISIL work?

LAMISIL 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.

What are the ingredients in LAMISIL?

Medicinal ingredient: terbinafine

Non-medicinal ingredients:

- **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

LAMISIL comes in the following dosage forms:

- Tablets: 250 mg
- Topical cream: 1 % w/w (10 mg/g)
- Topical spray solution: 1% w/w (10mg/g)

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.
- 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.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LAMISIL. Talk about any health conditions or problems you may have, including if you:

- have or have a history of 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 pregnant or plan to become pregnant while using LAMISIL.
- are breast-feeding or plan to breast-feed; 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.

Other warnings you should know about:

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

- **Tablets:**
    - Tell your doctor or pharmacist if you are taking or have recently oral contraceptives or birth control pills.

The following medicines may interact with LAMISIL:

- 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.

- **Cream and spray:**
    - No drug interactions are known to date.

How to take LAMISIL:

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.

Usual Dose:

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

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.

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 fungal 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.
  - 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.

- Relief of clinical symptoms usually occurs within a few days. Improper use or stopping the treatment early may cause a re-infection. 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:

- LAMISIL tablets: Symptoms caused by an overdose include headache, nausea, stomach pain and dizziness.
- LAMISIL cream or spray: No case of overdosage has been reported. If ingested by accident, symptoms similar to the LAMISIL tablets (listed above) are to be expected.

If you think you, or a person you are caring for, have taken too much LAMISIL, contact a healthcare professional, hospital emergency department, or regional Poison Control Center immediately, even if there are no symptoms.

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.

What are possible side effects from using LAMISIL?

LAMISIL tablets

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)*: 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, psoriasis-like skin eruptions (rash with silver coloured appearance), worsening of psoriasis, skin rash with flaking or peeling and hair loss.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Liver problems: sometimes fatal 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: sore throat, shivering, fever, mouth sore, weakness, unusual bleeding or bruising or getting infections frequently			✓
Serious allergic reactions (anaphylactic or serum sickness reactions) or infections: 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			✓
Skin reactions: rash, red skin, blistering of lips, eyes or mouth, peeling skin			✓
UNKNOWN/ NOT KNOWN			
Inflammation of the blood vessels (vasculitis) rash, fever, or appearance of purplish-red spots under the skin surface			✓
Inflammation of pancreas (pancreatitis): severe upper			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
stomach pain with radiation to the back			
Muscle breakdown (rhabdomyolysis): severe muscle cramps, aches and pain, or dark (red-brown) urine, feeling unusually tired			✓
Immune system disorders (lupus): facial rash, swollen joints or joint pain, muscle disorder, tiredness, fever			✓
Smell, taste, visual or hearing disorders or symptoms of depression			✓

These are not all the possible side effects you may have when taking LAMISIL. If you experience any side effects not listed here, tell your healthcare professional.

LAMISIL cream and spray

- The following side effects have been reported with LAMISIL cream and spray: 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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Allergic reaction (hypersensitivity): difficulty in breathing or swallowing, dizziness, swelling of the mouth, face, lips, tongue or throat	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad

enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at temperatures between 15°C and 30°C.
- Protect tablets from light.
- Keep out of the reach and sight of children.

If you want more information about LAMISIL:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

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LAMISIL is a registered trademark.