LAMISIL®
(terbinafine)
DermGel™, 1%

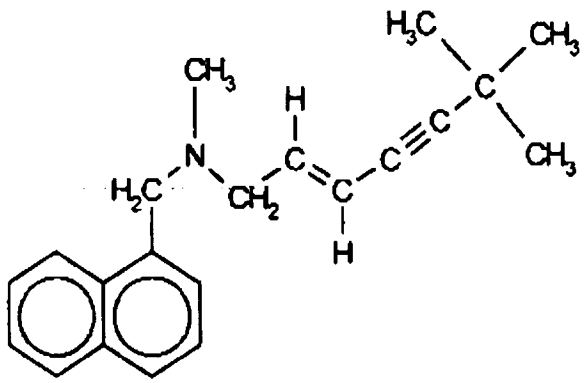
equivalent to 1.12%
terbinafine hydrochloride

FOR TOPICAL DERMATOLOGIC USE ONLY - - NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Lamisil® (terbinafine) DermGel™, 1% contains the synthetic antifungal compound, terbinafine. It is intended for topical dermatologic use only.

Chemically, terbinafine is (*E*)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine. The compound has the empirical formula $C_{21}H_{25}N$, a molecular weight of 291.44, and the following structural formula:



Terbinafine is a white to off-white fine crystalline powder. It is soluble in acetone, methanol and ethanol, and very slightly soluble in water (<0.001%).

Each gram of Lamisil® (terbinafine) DermGel™, 1% contains 10 mg of terbinafine in a gel of butylated hydroxytoluene NF, benzyl alcohol NF, sorbitan monolaurate NF, carbomer 934P NF, polysorbate 20 NF, isopropyl myristate NF, ethanol 11.3% (v/v), purified water, USP and sodium hydroxide Ph.Eur.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

In a study of 12 patients with tinea cruris/corporis, LAMISIL® (terbinafine) DermGel™, 1%, was applied once daily for 7 days to the diseased area(s) as well as a 2.5 cm margin of healthy skin. The mean daily application ranged from 20.4 to 92.1 mg. Terbinafine plasma levels up to 2.37 ng/mL were detected in 6 out of 12 patients on Day 1 and plasma levels up to 6.84 ng/mL were detected in 10 out of 12 patients on Day 7. These plasma levels are 37 times lower than those observed after repeated once a day oral administration of 250 mg terbinafine. The mean $AUC_{0\text{-}24}$ on Day 7 was 40.5 ng.h/mL.

In a study of 12 healthy volunteers, LAMISIL® (terbinafine) DermGel™, 1%, was applied once daily for 7 days to 20% of the body surface area with mean daily application of 67.5 ± 5.5 mg terbinafine. On Day 1, the highest measures plasma concentration was 4.38 ng/mL at 10 hours post dose. At Day 7 all subjects had quantifiable terbinafine concentrations with a maximum concentration of 9.72 ng/mL. The mean $AUC_{0\text{-}24}$ on Day 7 was 62.6 ng.h/mL. This is 0.6% of the $AUC_{0\text{-}24}$ (10,481 ng.h/mL) in healthy subjects following 250 mg orally for 28 days.

Distribution

The skin pharmacokinetics of Lamisil® (terbinafine) DermGel™, 1%, was compared to Lamisil (terbinafine hydrochloride) Cream, 1%, (equivalent to 0.89% terbinafine) in 36 volunteers with healthy skin. Groups of 6 subjects received a daily application for 1, 5, or 7 days. Approximately 5 mg of terbinafine was applied to two areas on the back, each measuring 12 x 8 cm. Penetration into stratum corneum was assessed by 5 sequential skin surface biopsies of 2.5 micron thickness. There was no significant difference in the total stratum corneum $AUC_{0\text{-}t}$ between Lamisil® (terbinafine) DermGel™, 1%, and Lamisil® (terbinafine hydrochloride) Cream, 1%, after 1.5 and 7 days of application.

Metabolism

It is unknown whether or not there is significant skin metabolism of topically applied terbinafine. Radiolabeled studies with oral dosage forms indicate that terbinafine is highly metabolized into a number of inactive metabolites which undergo conjugation and excretion into the urine. The primary metabolite seen in the urine (10% of the oral dose) is N-demethyl terbinafine. After topical application of Lamisil® (terbinafine) DermGel™, 1%, 2/12 patients and 6/12 healthy volunteers had detectable levels of the N-demethyl metabolite in the plasma at day 7 with maximum concentration being 0.99 ng/mL and 2.57 ng/mL, respectively.

Elimination

Based on a series of studies, the total stratum corneum half-life of terbinafine when absorbed through the skin is ~14-35 hours, depending on the topical dosage form of terbinafine. In a study comparing the Lamisil® (terbinafine) DermGel™,1%, with the Lamisil (terbinafine hydrochloride) Cream, 1%, dosage form, the total stratum corneum $t_{1/2}$ for terbinafine after Day 7 application of Lamisil® DermGel™ was 27.2 h vs. 35.2 h for Lamisil (terbinafine hydrochloride) Cream, 1%, ($p<0.05$). Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine, predominately as metabolites.

Microbiology

Terbinafine is a synthetic allylamine derivative. Terbinafine is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The allylamine derivatives, like benzylamines, act at an earlier step in the ergosterol biosynthesis pathway than the azole class of antifungal drugs. Depending on the concentration of the drug and the fungal species tested *in vitro*, terbinafine may be fungicidal. However, the clinical significance of the *in vitro* data is unknown.

Terbinafine has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Epidermophyton floccosum
Malassezia furfur
Trichophyton mentagrophytes
Trichophyton rubrum

CLINICAL STUDIES

In the majority of patients, relief of signs and symptoms at the end of study was demonstrated following a one week treatment period. Continued improvement occurred over a period of 2-7 weeks after treatment was concluded. In the following data presentations, the term "mycological cure" refers to those patients who had negative mycological results (*both* culture and microscopy - except in tinea (pityriasis) versicolor where only microscopy was used). The term "effective treatment" refers to an outcome with both a mycological cure and a *total* clinical score representing minimal residual signs and symptoms [less than or equal to 1 for tinea (pityriasis) versicolor and less than or equal to 2 for tinea corporis and tinea pedis with no more than a score of 1 in any sign or symptom]. The term "complete cure" refers to a case with both a mycological cure and a total clinical score of 0. The clinical score is the sum of the scores for each sign and symptom graded on a scale of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. All tinea (pityriasis) versicolor studies included clinical evaluation of erythema,

desquamation, and pruritus. All tinea pedis and tinea corporis studies included clinical evaluation of erythema, desquamation, pruritus, vesicles, encrustation and pustules.

Note: The following tables are extracted from the final reports for each study. The Intent-to-Treat Populations were used to generate these tables where EOT is End-of-Treatment (week 1) and EOS is End-of-Study (week 8 or last visit before leaving study):

A. Tinea (pityriasis) versicolor

In two studies of Lamisil® (terbinafine) DermGel™,1%, applied once daily for 1 week in the treatment of tinea (pityriasis) versicolor (Lamisil: N=114, Vehicle: N=70), the combined efficacy results were as follows:

Response	Therapy	EOT	EOS
Mycological Cure	Lamisil	65%	74%
	Vehicle	28%	11%
Effective Treatment	Lamisil	50%	73%
	Vehicle	21%	11%
Complete Cure	Lamisil	27%	68%
	Vehicle	9%	11%

Tinea (pityriasis) versicolor is a non-contagious infestion of the glabrous skin caused by *Pityrosporum orbiculare* (*Malassezia furfur*). The commensal organism is part of the normal skin flora. In susceptible individuals the condition is often recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending upon individual skin type and incidental sun exposure. The rate of recurrence of infection is variable.

B. Tinea Pedis

The results of two studies using Lamisil® (terbinafine) DermGel™,1%, applied once daily:

Response	Therapy	EOT	EOS
Mycological Cure	Lamisil	33%	87%
	Vehicle	20%	28%
Effective Treatment	Lamisil	11%	72%
	Vehicle	11%	21%
Complete Cure	Lamisil	0%	39%
	Vehicle	3%	12%

C. Tinea Corporis

Studies presented adequately support the superiority of Lamisil® (terbinafine) DermGel™,1%, compared to vehicle in the treatment of tinea corporis.

INDICATIONS AND USAGE

Lamisil® (terbinafine) DermGel™,1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*), tinea pedis (athlete's foot) or tinea corporis (ringworm), due to *Trichophyton rubrum, Trichophyton mentagrophytes*, or *Epidermophyton floccosum* (See **DOSAGE AND ADMINISTRATION**). Diagnosis of disease should be confirmed either by culture (except *Malassezia furfur* , formerly *Pityrosporum ovale)* or examination of scrapings from infected tissue mounted in a solution of potassium hydroxide.

CONTRAINDICATIONS

Lamisil® (terbinafine) DermGel™ ,1%, is contraindicated in individuals who have known or suspected hypersensitivity to terbinafine or any other of its components.

WARNINGS

Lamisil® (terbinafine) DermGel™,1%, is not for ophthalmic, oral, or intravaginal use.

PRECAUTIONS

General: Lamisil® (terbinafine) DermGel™,1%, contains 11.3% v/v alcohol. If irritation or sensitivity develops with the use of Lamisil® (terbinafine) DermGel™, 1%, treatment should be discontinued and appropriate therapy instituted.

Lamisil® (terbinafine) DermGel™,1%, may be irritating to the eyes.

Information for Patients: *The patient should be told to:*

1. Use Lamisil® (terbinafine) DermGel™,1%, as directed by the physician, and avoid contact with the eyes, nose, mouth, or other mucous membranes. In case of accidental contact with the eyes, rinse eyes thoroughly with running water and consult a physician if any symptoms persist.

2. Apply Lamisil® (terbinafine) DermGel™,1%, once daily.

3. Cleanse and dry the affected areas thoroughly before applying Lamisil® (terbinafine) DermGel™,1%. Sufficient gel should be applied to cover the affected skin and surrounding area.

4. Use the medication for the full treatment time, even though symptoms may have improved.

5. Inform the physician if the area of application shows signs of increased irritation or possible sensitization (redness, itching, burning, blistering, swelling, or oozing).

6. Notify the physician if there is no improvement after the full course of treatment.

7. Avoid covering the affected areas with dressings, unless otherwise directed by the physician.

Drug Interactions

Potential interactions between Lamisil® (terbinafine) DermGel™,1%, and other drugs have not been systematically evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 28-month oral carcinogenicity study in rats, a marginal increase in the incidence of liver tumors was observed in males at the highest dose level, 69 mg/kg/day (in terms of mg/m^2/day equivalent to 41 times the maximum potential exposure at the recommended topical human dose*). There was no dose-related trend, and the mid-dose male rats, 20 mg/kg/day (in terms of mg/m^2/day equivalent to 12 times the maximum potential exposure at the recommended topical human dose*), did not have any liver tumors. No increased incidence in liver tumors was noted in female rats at dose levels up to 97 mg/kg/day (in terms of mg/m^2/day equivalent to 58 times the maximum potential exposure at the recommended topical human dose*), or in male or female mice treated orally for 23 months at doses up to 156 mg/kg/day (in terms of mg/m^2/day equivalent to 47 times the maximum potential exposure at the recommended topical human dose*).

A wide range of oral *in vivo* studies in mice, rats, dogs and monkeys and *in vitro* studies using rat, monkey and human hepatocytes suggest that the development of liver tumors in the high-dose male rats may be associated with peroxisome proliferation and support the conclusion that this is a rat-specific finding.

The results of a variety of *in vitro* (mutations in *E. coli* and *Salmonella typhimurium*, DNA repair in rat hepatocytes, mutagenicity in Chinese hamster fibroblasts, chromosome aberration and sister chromatid exchanges in Chinese hamster lung cells), and *in vivo* (chromosome aberration in Chinese hamsters, micronucleus test in mice) genotoxicity tests gave no evidence of a mutagenic or clastogenic potential and demonstrated the absence of tumor-initiating or cell-proliferating activity.

Oral reproduction studies in rats at doses up to 300 mg/kg/day (in terms of mg/m^2/day equivalent to 180 times the maximum potential exposure at the recommended topical human dose*) did not reveal any specific effects on fertility or other reproductive parameters. Intravaginal application of terbinafine hydrochloride at 150 mg/day (in terms of mg/m^2/day equivalent to 101 times the maximum potential exposure at the recommended topical human dose*) in pregnant rabbits did not increase the incidence of abortions, premature deliveries or fetal abnormalities.

Pregnancy

Pregnancy Category B: Oral doses of terbinafine hydrochloride up to 300 mg/kg/day (in terms of mg/m^2/day equivalent to 180 and 404 times the maximum potential exposure at the recommended topical human dose*) during organogenesis in rats and rabbits, respectively, were not teratogenic. Similarly, a subcutaneous study in rats at doses up to 100 mg/kg/day (in terms of mg/m^2/day equivalent to 60 times the maximum potential exposure at the recommended topical human dose*) and a percutaneous study in rabbits, including doses up to 150 mg/kg/day (in terms of mg/m^2/day equivalent to 202 times the maximum potential exposure at the recommended topical human dose*) did not reveal any teratogenic potential. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Lamisil® (terbinafine) DermGel™, 1%, should be used only if clearly indicated during pregnancy.

* The above comparisons between oral animal doses and the maximum potential exposure at the recommended topical human dose are based upon the application to human skin of 0.1 mg of terbinafine/cm^2 once daily, the assumption of average human cutaneous exposure of 100 cm^2 (assuming the use of 1 gram of Lamisil® gel/dose), and the theoretical maximum human cutaneous absorption of 100%.

Nursing Mothers: After a single oral dose of 500 mg of terbinafine hydrochloride to two volunteers, the total dose of terbinafine secreted in human milk during the 72-hour post-dosing period was 0.65 mg in one person and 0.15 mg in the other. The total excretion of terbinafine in human milk was 0.13% and 0.03% of the administered dose, respectively. This 500 mg dose represents about 50 times the maximum potential percutaneous exposure as described in the previous paragraph. The concentrations of the *N*-demethylated metabolite measured in the milk of these two volunteers were below the detection limit (150 ng/mL) of the assay.

Because of the small amount of data on human neonatal exposure, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Nursing mothers should avoid application of Lamisil® (terbinafine) DermGel™,1%, to the breast.

Pediatric Use: The safety and efficacy of Lamisil® (terbinafine) DermGel™,1%, have not been established in pediatric patients.

ADVERSE REACTIONS

Clinical Trials

In clinical trials, none of the 239 patients treated with Lamisil® (terbinafine) DermGel™,1%, discontinued therapy due to adverse events. For Lamisil® (terbinafine) DermGel™,1%, treated patients, adverse reactions thought to be possibly, probably, or definitely related to drug therapy included application site reactions (burning or irritation) (2.0%), skin disorder (2.0%), pruritus (1.7%) and skin discoloration (1.3%).

OVERDOSAGE

Clinical experience regarding overdose with Lamisil® is limited. Doses up to 5 grams of terbinafine hydrochloride (equivalent to approximately fifteen 30 gram tubes of Lamisil® (terbinafine) DermGel™,1%) have been taken without inducing serious adverse reactions. The symptoms of overdose associated with oral terbinafine hydrochloride included nausea, vomiting, abdominal pain, dizziness, rash, urinary frequency and headache. There has been no experience of overdose with topical formulations of terbinafine. However, the alcohol content (11.3%) of Lamisil® (terbinafine) DermGel™,1%, has to be taken into account.

When Lamisil® (terbinafine) DermGel™,1%, was administered as a single oral dose at 10 or 25 mL/kg (100 and 250 mg/kg, respectively) to rats and mice, no deaths or other drug-related toxicities were observed.

DOSAGE AND ADMINISTRATION

For the treatment of tinea (pityriasis) versicolor, tinea corporis and tinea pedis Lamisil® (terbinafine) DermGel™,1%, is applied once daily for seven days. The affected areas should be cleansed and dried thoroughly before applying Lamisil® (terbinafine) DermGel™,1%. Sufficient amounts should be applied to cover the treatment area(s) thoroughly, including the affected skin and surrounding area (See **CLINICAL STUDIES**).

HOW SUPPLIED

Lamisil® (terbinafine) DermGel™, 1%
Tubes of 5 grams (NDC ....-...-..)
Tubes of 15 grams (NDC ....-...-..)
Tubes of 30 grams (NDC ....-...-..)

Store at or below 25 °C (77°F).

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Novartis Pharmaceuticals Corporation
East Hanover, N.J.