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PACKAGE INSERT

LAMISIL® Solution, 1%

(terbinafine hydrochloride solution)

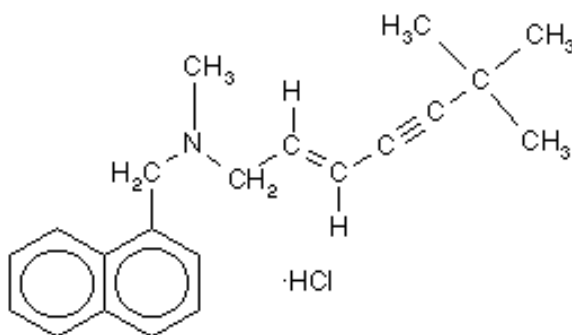
Rx Only

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

DESCRIPTION

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

Chemically, terbinafine hydrochloride is (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The compound has the empirical formula $C_{21}H_{26}ClN$, a molecular weight of 327.90, and the following structural formula:



Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

Each gram of Lamisil® Solution, 1% (terbinafine hydrochloride solution) contains 10 mg of terbinafine hydrochloride in a solution of cetomacrogol 1000, ethanol (28.7%), propylene glycol, and purified water, USP.

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CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

In a study of 10 patients with tinea cruris, once daily application of Lamisil® Solution, 1% (terbinafine hydrochloride solution) for 7 days (total amount of terbinafine hydrochloride applied averaged 0.8 g) resulted in plasma concentrations of terbinafine of up to 21 ng/mL on day 7, representing approximately 2% of plasma concentrations achieved with a 250 mg terbinafine hydrochloride tablet. Plasma concentrations of the N-demethylated metabolite of terbinafine ranged up to 14 ng/mL in these patients. In subjects with healthy skin, neither the parent nor the N-demethylated metabolite were detected in the plasma following once daily dosing for seven days with 0.3g of 1% terbinafine hydrochloride solution.

Distribution

The skin pharmacokinetics of Lamisil® Solution, 1% (terbinafine hydrochloride solution), delivered by spray was compared to the 1% Cream in 36 healthy subjects following both single and multiple applications (approximately 5 mg of terbinafine hydrochloride was applied to roughly a 190 cm² area on the back). Maximum mean total stratum corneum drug concentrations (C_{max}) averaged 720 and 810 ng/cm² on days 1 and 7, respectively. No significant differences in total stratum corneum AUC (area under the curve), C_{max} and half-life were seen between the 1 % spray and the 1 % cream after 1 or 7 days of treatment. Similar skin levels of terbinafine are achieved by delivery of Lamisil® Solution, 1% (terbinafine hydrochloride solution) from the spray bottle or from application of Lamisil® 1% Cream (terbinafine hydrochloride cream).

Metabolism

It is unknown whether or not there is any significant skin metabolism of topically applied terbinafine. Radiolabeled studies with oral dosage forms indicate that terbinafine is highly metabolized into a number of 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.

Elimination

The half-life of terbinafine when absorbed through the skin, regardless of the method of topical administration, is ~21 hours. Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine, predominately as metabolites.

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Microbiology

Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine hydrochloride is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The allylamine derivatives, like the 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 hydrochloride may be fungicidal. However, the clinical significance of *in vitro* data is unknown.

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

Epidermophyton floccosum
Malassezia furfur
Trichophyton mentagrophytes
Trichophyton rubrum

The following *in vitro* data are available; **but their clinical significance is unknown**. *In vitro*, terbinafine exhibits satisfactory MIC's against most strains of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Microsporum canis
Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum

INDICATIONS AND USAGE

Prescription Lamisil® Solution, 1% (terbinafine hydrochloride solution) is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*). Diagnosis of disease should be confirmed by direct microscopic examination of scrapings from infected tissue mounted in a solution of potassium hydroxide.

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CONTRAINDICATIONS

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

WARNINGS

Lamisil® Solution, 1% (terbinafine hydrochloride solution) is not for ophthalmic, oral, or intravaginal use.

PRECAUTIONS

General

Lamisil® Solution, 1% (terbinafine hydrochloride solution) contains 28.7% alcohol. If irritation or sensitivity develops with the use of Lamisil® Solution, 1% (terbinafine hydrochloride solution) treatment should be discontinued and appropriate therapy instituted.

Lamisil® Solution, 1% (terbinafine hydrochloride solution) may be irritating to the eyes.

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

1. Use Lamisil® Solution, 1% (terbinafine hydrochloride solution) as directed by the physician and avoid contact with the eyes, nose, mouth, or other mucous membranes. The spray form should not be used on the face. 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® Solution, 1% (terbinafine hydrochloride solution) twice daily.
3. Cleanse and dry the affected areas thoroughly before applying Lamisil® Solution. Sufficient solution should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area.
4. Use the medication for the full treatment time (1 week) 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).

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6. Notify the physician if there is no improvement after one week of treatment.
7. Avoid the use of occlusive dressings unless otherwise directed by the physician.

Drug Interactions

Potential interactions between Lamisil® Solution, 1% (terbinafine hydrochloride solution) 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/m²/day equivalent to 34 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/m²/day equivalent to 10 times the maximum potential exposure at the recommended topical human dose*) did not have any 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/m²/day equivalent to 47 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/m²/day equivalent to 38 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*, 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.

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Oral reproduction studies in rats at doses up to 300 mg/kg/day (in terms of mg/m²/day equivalent to 146 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/m²/day equivalent to 165 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/m²/day equivalent to 146 and 329 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/m²/day equivalent to 49 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/m²/day equivalent to 329 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® Solution, 1% (terbinafine hydrochloride solution) should be used only if clearly indicated during pregnancy.

- * The above comparisons between oral animal doses and maximum potential exposure at the recommended human topical dose are based upon the application to human skin of 0.1 mg of terbinafine/cm² twice daily, the assumption of average human cutaneous exposure of 100 cm² (assuming the use of 1 gram of Lamisil® Solution/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 percutaneous exposure as described in the previous paragraph. The concentrations of the N-demethylated metabolite measured in the human milk of these two volunteers were below the detection limit of the assay used (150 ng/mL of milk).

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.

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Nursing mothers should avoid application of Lamisil® Solution, 1% (terbinafine hydrochloride solution) to the breast.

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

ADVERSE REACTIONS

Clinical Trials

For Lamisil® Solution-treated patients, adverse reactions thought to be possibly, probably, or definitely related to drug therapy included application site reactions (burning or irritation) (1.3%), itching (1.1%), skin exfoliation (1.0%) and erythematous rash (0.9%). In clinical trials with Lamisil Solution in dermatophyte infections, 2 (0.2%) of 898 patients treated with Lamisil® Solution, 1% (terbinafine hydrochloride solution) and 2 (0.6%) of 306 patients treated with placebo (vehicle) discontinued therapy due to adverse events..

OVERDOSAGE

Present clinical experience regarding overdose with Lamisil® is limited. Up to 5 grams of terbinafine hydrochloride tablets (equivalent to approximately 17 bottles of Lamisil® Solution, 1% (terbinafine hydrochloride solution) have been taken without inducing severe or life-threatening 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 (28.7% alcohol) of Lamisil® Solution, 1% (terbinafine hydrochloride solution) has to be taken into account.

Terbinafine overdosage in rats and mice by the oral and intravenous routes of drug administration has produced sedation, drowsiness, ataxia, dyspnea, exophthalmus, and piloerection. The majority of deaths in animals occurred following oral administration of doses exceeding 3 g/kg or following 200 mg/kg administered intravenously. In rabbits, overdosage produced erythema, edema, and scale formation following topical administration of doses in excess of 1.5 g/kg.

When 1% terbinafine hydrochloride solution was administered as a single oral dose at 20 or 25 mL/kg (200 and 250 mg/kg, respectively) to rats and mice, no deaths or other drug-related toxicities were observed.

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DOSAGE AND ADMINISTRATION

Lamisil® Solution, 1% (terbinafine hydrochloride solution) is applied twice daily for one week. The affected areas should be cleansed and dried thoroughly before applying Lamisil® Solution, 1% (terbinafine hydrochloride solution). Sufficient solution should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area (See **CLINICAL STUDIES**). If successful outcome is not achieved during the post treatment period, the diagnosis should be reviewed.

CLINICAL STUDIES

In the majority of patients, relief of signs and symptoms begins within the one week treatment period with continued improvement occurring over a period of 2-7 weeks after treatment has concluded. In the following data presentations, the terms “mycological cure” refers to those patients evaluated at a specific timepoint who had negative mycoscopy results. 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). 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. The term “complete cure” refers to a case with both a mycological cure and a total clinical score of 0.

Note: The following table is 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):

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Tinea (pityriasis) Versicolor

In two studies of Lamisil® Solution, 1% (terbinafine hydrochloride solution), applied twice daily for 1 week in the treatment of tinea (pityriasis) versicolor (Lamisil: N=173, Vehicle: N=81), the combined efficacy results were as follows:

Response	Therapy	EOT	EOS
Mycological Cure	Lamisil	50.6%	78.8%
	Vehicle	43.6%	35.8%
Effective Treatment	Lamisil	39.3%	74.3%
	Vehicle	24.1%	29.6%
Complete Cure	Lamisil	19.4%	57.6%
	Vehicle	11.4%	27.2%

HOW SUPPLIED

Lamisil® Solution, 1% (terbinafine hydrochloride solution) is supplied in a 30 mL pump spray bottle containing 290 mg of terbinafine hydrochloride (NDC 0078-0328-82) with a spray-pump assembly, which will also function upside-down, and protective cap.

Store at 5 °C to 25 °C (41 °F to 77 °F); do not refrigerate.