

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-071

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lamisil® Oral Granules safely and effectively. See full prescribing information for Lamisil Oral Granules.

Lamisil® (terbinafine hydrochloride)

Initial U.S. Approval: 1992

-----**INDICATIONS AND USAGE**-----

Lamisil Oral Granules is an allylamine antifungal indicated for the treatment of tinea capitis in patients 4 years of age and older. (1)

-----**DOSAGE AND ADMINISTRATION**-----

Take once a day with food for 6 weeks (dose based on body weight). The entire contents of each packet of granules should be sprinkled on a spoonful of non-acidic food (for example, pudding or mashed potatoes) and swallowed in its entirety. (2)

Table 1: Dosage by Body Weight

<25 kg	125 mg/day
25-35 kg	187.5 mg/day
>35 kg	250 mg/day

-----**DOSAGE FORMS AND STRENGTHS**-----

Laminated packet containing approximately 30 film-coated granules, corresponding to a single total dose of 125 mg (terbinafine base equivalent). (3)

Laminated packet containing approximately 45 film-coated granules, corresponding to a single total dose of 187.5 mg (terbinafine base equivalent). (3)

-----**CONTRAINDICATIONS**-----

Lamisil Oral Granules is contraindicated in individuals with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Cases of liver failure, some leading to death or liver transplant, have

occurred with the use of oral terbinafine. Pretreatment serum transaminase (ALT and AST) tests are advised for all patients before taking Lamisil Oral Granules. (5.1, 5.2)

- Severe neutropenia has been reported. If the neutrophil count is $\leq 1,000$ cells/mm³, Lamisil Oral Granules should be discontinued. (5.3)
- Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with oral terbinafine use. If progressive skin rash occurs, treatment with Lamisil Oral Granules should be discontinued. (5.4)

-----**ADVERSE REACTIONS**-----

Common (>3% in patients treated with Lamisil Oral Granules) reported adverse events include: nasopharyngitis, headache, pyrexia, cough, vomiting, upper respiratory tract infection, upper abdominal pain, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1 888 669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

Drug interactions have been noted with drugs metabolized by the CYP450 2D6 isozyme, including desipramine. Drug interactions have also been noted with cimetidine, fluconazole, cyclosporine, rifampin, and caffeine. (7.1)

-----**USE IN SPECIFIC POPULATIONS**-----

- Pregnancy**
It is recommended that Lamisil not be initiated during pregnancy. (8.1)
- Nursing Mothers**
Treatment with Lamisil is not recommended in nursing mothers. (8.3)
- Pediatric Use**
Lamisil Oral Granules has been studied in children 4 to 12 years old with tinea capitis. (8.4)
- Geriatrics**
Lamisil Oral Granules has not been studied in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

Lamisil (terbinafine hydrochloride) Oral Granules is indicated for the treatment of tinea capitis in patients four years of age and older.

2 DOSAGE AND ADMINISTRATION

Lamisil (terbinafine hydrochloride) Oral Granules should be taken once a day for 6 weeks based upon body weight [See Table 1]. Sprinkle the contents of each packet on a spoonful of pudding or other soft, non-acidic food such as mashed potatoes and swallow the entire spoonful (without chewing); do not use applesauce or fruit-based foods. Take with food. If two packets (250 mg) are required with each dose, either the content of both packets may be sprinkled on one spoonful, or the contents of both packets may be sprinkled on two spoonfuls of non-acidic food as directed above.

Table 1: Dosage by Body Weight

<25 kg	125 mg/day
25-35 kg	187.5 mg/day
>35 kg	250 mg/day

3 DOSAGE FORMS AND STRENGTHS

Lamisil (terbinafine hydrochloride) Oral Granules are supplied in cartons containing 14 laminated aluminum packets. Each packet contains approximately either 30 or 45 off-white to yellowish, round, biconvex, film-coated granules, corresponding to a single total dose of 125 mg or 187.5 mg (terbinafine base equivalent) per packet.

Lamisil Oral Granules are manufactured using a tablet compression process, followed by film-coating. The film-coated granules are off-white to yellowish, round, biconvex, each having a diameter of approximately 2.1 mm. Each individual granule contains 4.6875 mg of terbinafine hydrochloride, corresponding to 4.167 mg of terbinafine base.

4 CONTRAINDICATIONS

Lamisil (terbinafine hydrochloride) Oral Granules is contraindicated in individuals with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis.

5 WARNINGS AND PRECAUTIONS**5.1 HEPATOTOXICITY**

Cases of liver failure, some leading to death or liver transplant, have occurred with the use of oral terbinafine during postmarketing experience in individuals with and without pre-existing liver disease. In the majority of liver cases reported, the patients had serious underlying systemic conditions. The severity of hepatic events and/or their outcome may be worse in patients with active or chronic liver disease. Treatment with Lamisil Oral Granules should be discontinued if biochemical or clinical evidence of liver injury develops.

Lamisil Oral Granules is not recommended for patients with chronic or active liver disease. Before prescribing Lamisil Oral Granules, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Pretreatment serum transaminase (ALT and AST) tests are advised for all patients before taking Lamisil Oral Granules. Patients prescribed Lamisil Oral Granules and/or their guardians should be warned to report immediately to their physician

any symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine or pale stools. Patients with these symptoms should discontinue taking Lamisil Oral Granules, and the patient's liver function should be immediately evaluated.

5.2 MONITORING LABORATORY TESTS

Pretreatment serum transaminase (ALT and AST) tests are advised for all patients before taking Lamisil Oral Granules.

5.3 HEMATOLOGICAL

Transient decreases in absolute lymphocyte counts (ALC) have been observed in clinical trials. In placebo-controlled trials, 8/465 subjects receiving Lamisil Tablets (1.7%) and 3/137 subjects receiving placebo (2.2%) had decreases in ALC to below 1000/mm³ on two or more occasions. In patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts if treatment will exceed six weeks. Cases of severe neutropenia have been reported; these were reversible upon discontinuation of terbinafine, with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is $\leq 1,000$ cells/mm³, Lamisil Oral Granules should be discontinued and supportive management started.

5.4 SKIN REACTIONS

There have been post marketing reports of serious skin reactions (e.g., Stevens-Johnson Syndrome and toxic epidermal necrolysis) with oral terbinafine. If progressive skin rash occurs, treatment with Lamisil Oral Granules should be discontinued.

5.5 RENAL FUNCTION

In patients with renal impairment (creatinine clearance < 50 mL/min), the use of Lamisil Oral Granules has not been adequately studied [see *Clinical Pharmacology* (12.3)].

5.6 LUPUS ERYTHEMATOSUS

During postmarketing experience, precipitation and exacerbation of cutaneous and systemic lupus erythematosus have been reported in patients taking oral terbinafine. Therapy should be discontinued in patients with clinical signs and symptoms suggestive of lupus erythematosus.

6. ADVERSE REACTIONS

6.1 CLINICAL STUDIES EXPERIENCE

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Lamisil (terbinafine hydrochloride) Oral Granules

The data described below reflect exposure to terbinafine including 1042 subjects exposed for a median of 42 days. Lamisil Oral Granules was studied in 2 active-controlled trials (n=1042). The population was children aged 4 to 12 years old, 64% male and 36% female, 21% Caucasian, 47% Black, 32% Other. Baseline disease (dermatophyte) characteristics of subjects included 49% having *T. tonsurans*, 15% *T. violaceum*, 15% *M. canis*, 2% *M. audouinii*, and 1% others. Subjects received once daily, for 6 weeks, oral doses of Lamisil Oral Granules based on body weight: < 25 kg 125 mg/day, 25-35kg 187.5 mg/day, and > 35 kg 250 mg/day.

Adverse events reported in the 2 trials are listed in the table below.

Table 2 Adverse Events ($\geq 1\%$) in the Tinea Capitis Trials

	Lamisil [®] Oral Granules (%) N=1042	Griseofulvin oral suspension (%) N=507
Nasopharyngitis	10	11
Headache	7	8
Pyrexia	7	6
Cough	6	5
Vomiting	5	5
Upper respiratory tract infection	5	5
Upper abdominal pain	4	4
Diarrhea	3	4
Influenza	2	1
Abdominal pain	2	1
Pharyngolaryngeal pain	2	2
Nausea	2	2
Rash	2	2
Rhinorrhea	2	0
Nasal congestion	2	1
Pruritus	1	1
Toothache	1	1

In the pooled pivotal trials, 2% (17/1042) of subjects in the terbinafine group and 2% (6/507) in the griseofulvin group experienced discontinuation of study drug due to adverse events. The most common categories of adverse events causing discontinuation in those exposed to terbinafine included gastrointestinal disorders, skin and subcutaneous disorders, and infections and infestations.

No ophthalmologic safety signal was identified in the pooled pivotal trials. Ophthalmologic assessments included dilated funduscopy to assess for refractile bodies in the retina, visual acuity assessment, and color vision testing. Of the 940 subjects in the terbinafine group and 471 subjects in the griseofulvin group who completed dilated funduscopy at post-treatment visits, none of the subjects were found to have refractile bodies of the retina at baseline or end of treatment. For visual acuity, 1% (11/837) of subjects treated with terbinafine and 2% (7/426) of subjects treated with griseofulvin showed a doubling of visual angle after 6 weeks of treatment, while 2% (15/837) treated with terbinafine and 3% (12/426) treated with griseofulvin showed a halving of the visual angle after 6 weeks of treatment. Of subjects who completed yellow-blue color vision assessment for acquired defects, 5% (13/262) of subjects treated with terbinafine and 6% (8/129) of subjects treated with griseofulvin had color confusion on more than one symbol at week 6 than at baseline, while 13% (33/262) of subjects treated with terbinafine and 13% (17/129) of subjects treated with griseofulvin identified more symbols correctly at week 6 than at baseline.

Lamisil (terbinafine hydrochloride) Tablets

Adverse events reported in three US/Canadian placebo-controlled trials included diarrhea (6%), rashes (6%), dyspepsia (4%), nausea (3%), liver abnormalities (3%), pruritus (3%), taste disturbances (3%), abdominal pain (2%), and urticaria (1%).

Changes in the ocular lens and retina have been reported following the use of Lamisil Tablets in clinical trials in adult subjects with onychomycosis. The clinical significance of these changes is unknown.

6.2 POSTMARKETING EXPERIENCE

The following adverse events have been identified during postapproval use of Lamisil. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse events reported with oral terbinafine use include: idiosyncratic and symptomatic hepatic injury and, cases of liver failure, some leading to death or liver transplant, serious skin reactions, severe neutropenia, thrombocytopenia, agranulocytosis, pancytopenia, anemia, angioedema and allergic reactions (including anaphylaxis) [see *Warnings and Precautions (5.1), (5.3), and (5.4)*].

Psoriasiform eruptions or exacerbation of psoriasis, acute generalized exanthematous pustulosis and precipitation and exacerbation of cutaneous and systemic lupus erythematosus have been reported. Oral terbinafine may cause taste disturbance (including taste loss) which usually recovers within several weeks after discontinuation of the drug. There have been reports of prolonged (greater than one year) taste disturbance. Taste disturbances have been reported to be severe enough to result in decreased food intake leading to significant and unwanted weight loss.

Other adverse reactions which have been reported include malaise, fatigue, arthralgia, myalgia, vomiting, acute pancreatitis, rhabdomyolysis, reduced visual acuity, visual field defects, and hair loss. Adverse events reported spontaneously since the drug was marketed include altered prothrombin time (prolongation and reduction) in patients concomitantly treated with warfarin.

7 DRUG INTERACTIONS

7.1 DRUG-DRUG INTERACTIONS

In vivo studies have shown that terbinafine is an inhibitor of the CYP450 2D6 isozyme. Drugs predominantly metabolized by the CYP450 2D6 isozyme include the following drug classes: tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers, antiarrhythmics class 1C (e.g., flecainide and propafenone) and monoamine oxidase inhibitors Type B. Coadministration of Lamisil (terbinafine hydrochloride) Oral Granules should be done with careful monitoring and may require a reduction in dose of the 2D6-metabolized drug. In a study to assess the effects of terbinafine on desipramine in healthy volunteers characterized as normal metabolizers, the administration of terbinafine resulted in a 2-fold increase in C_{max} and a 5-fold increase in AUC. In this study, these effects were shown to persist at the last observation at 4 weeks after discontinuation of Lamisil. In studies in healthy subjects characterized as extensive metabolizers of dextromethorphan, terbinafine increases the dextromethorphan/dextrophan metabolite ratio in urine by 16- to 97-fold, on average. *In vitro* studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin, cyclosporine, cisapride and fluvastatine.

In vivo drug-drug interaction studies conducted in healthy volunteer subjects showed that terbinafine does not affect the clearance of antipyrine or digoxin. Terbinafine decreases the clearance of caffeine by 19%. Terbinafine increases the clearance of cyclosporine by 15%.

The influence of terbinafine on the pharmacokinetics of fluconazole, trimethoprim, sulfamethoxazole, zidovudine or theophylline was not considered to be clinically significant.

Co-administration of a single dose of fluconazole (100 mg) with a single dose of terbinafine resulted in a 52% and 69% increase in terbinafine C_{max} and AUC, respectively. Fluconazole is an inhibitor of CYP 2C9 and CYP 3A enzymes. Based on this finding, it is likely, that other inhibitors of both CYP2C9 and CYP3A4 (e.g., ketoconazole, amiodarone) may also lead to a substantial increase in the systemic exposure (C_{max} and AUC) of terbinafine.

There have been spontaneous reports of increase or decrease in prothrombin times in patients concomitantly taking oral terbinafine and warfarin, however, a causal relationship between Lamisil Tablets and these changes has not been established.

Terbinafine clearance is increased 100% by rifampin, a CYP450 enzyme inducer, and decreased 33% by cimetidine, a CYP450 enzyme inhibitor. Terbinafine clearance is unaffected by cyclosporine. There is no information available from adequate drug-drug interaction studies with the following classes of drugs: oral contraceptives, hormone replacement therapies, hypoglycemics, phenytoins, thiazide diuretics, and calcium channel blockers.

7.2 FOOD INTERACTIONS

An evaluation of the effect of food on Lamisil (terbinafine hydrochloride) Oral Granules was not conducted. However, in the clinical trials, Lamisil (terbinafine hydrochloride) Oral Granules was administered with food [see *Dosage and Administration* (2)].

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Pregnancy Category B.

Oral reproduction studies have been performed in rabbits and rats at doses up to 300 mg/kg/day [12x to 23x the Maximum Recommended Human Dose (MRHD), in rabbits and rats, respectively, based on body surface area (BSA) comparisons] and have revealed no evidence of impaired fertility or harm to the fetus due to terbinafine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because treatment of onychomycosis can be postponed until after pregnancy is completed, it is recommended that Lamisil (terbinafine hydrochloride) Oral Granules not be initiated during pregnancy.

8.3 NURSING MOTHERS

After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with Lamisil Oral Granules is not recommended in nursing mothers.

8.4 PEDIATRIC USE

Lamisil Oral Granules was studied in two randomized, active-controlled trials in which 1021 subjects having a clinical diagnosis of tinea capitis confirmed by KOH microscopy were treated with Lamisil Oral Granules at the labeled dose for up to 6 weeks. The most common adverse events were nasopharyngitis, headache, pyrexia, cough, vomiting, and upper respiratory tract infection [see *Adverse Reactions* (6.1)].

8.5 GERIATRIC USE

Lamisil Oral Granules has not been studied in geriatric patients.

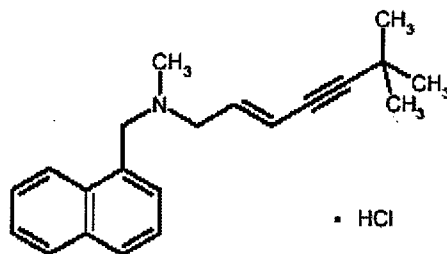
10 OVERDOSAGE

Clinical experience regarding overdose with oral terbinafine is limited. Doses up to 5 grams in adults (20 times the therapeutic daily adult dose) have been reported without inducing serious adverse reactions. The symptoms of overdose included nausea, vomiting, abdominal pain, dizziness, rash, frequent urination, and headache.

11 DESCRIPTION

Lamisil (terbinafine hydrochloride) Oral Granules 125 mg and 187.5 mg contain the synthetic allylamine antifungal compound, terbinafine hydrochloride.

Chemically, terbinafine hydrochloride is (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. It has the empirical formula $C_{21}H_{26}ClN$ with 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 packet of Lamisil Oral Granules contains:

Active Ingredients: terbinafine hydrochloride (equivalent to 125 mg or 187.5 mg terbinafine base)

Inactive Ingredients: basic butylated methacrylate copolymer, colloidal silicon dioxide NF, dibutyl sebacate NF, hypromellose USP, magnesium stearate NF, microcrystalline cellulose NF, nitrogen NF (filling gas), polyethylene glycol NF, sodium lauryl sulfate NF, and sodium starch glycolate NF.

12 CLINICAL PHARMACOLOGY

12.1 MECHANISM OF ACTION

Terbinafine is an allylamine antifungal [see *Clinical Pharmacology* (12.4)].

12.2 PHARMACODYNAMICS

The pharmacodynamics of Lamisil[®] (terbinafine hydrochloride) Oral Granules is unknown.

12.3 PHARMACOKINETICS

The pharmacokinetics in children 4 to 8 years of age with tinea capitis was investigated in a pharmacokinetic study after single and repeated (for 42 days) oral administration of Lamisil Oral Granules (N=16), once daily, using the body weight groups and doses described in section 2.2. The systemic exposure (C_{max} and AUC_{0-24}) of terbinafine in children had a relatively high inter-individual variability (ranging from 36 % to 64 %). At steady state the AUC_{0-24} increased by a mean factor of 1.9 to 2.1 across doses. The mean (SD) effective half-life obtained from the observed accumulation was 26.7 (13.8) hrs and 30.5 (9.3) hrs for the 125 mg and 187.5 mg doses, respectively.

Systemic exposure to terbinafine in the children did not exceed the highest values of the systemic exposure in adults receiving repeated once daily doses of 250 mg Lamisil (terbinafine) Tablets. A population pharmacokinetic evaluation of oral terbinafine that included children 4-12 years of age and adults 18-45 years of age (N=113) found that clearance (CL/F) of terbinafine is dependent on body

weight in a nonlinear manner. For a typical child of 25 kg CL/F was predicted to be 19 L/h and for a typical adult of 70 kg body weight it was predicted to be 27 L/h. Over the weight range for pediatric patients included in the analysis (14.1 kg-68 kg), the predicted CL/F ranged between 15.6 – 26.7 L/hr. In plasma, terbinafine is >99% bound to plasma proteins. Prior to excretion, terbinafine is rapidly and extensively metabolized by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. No metabolites have been identified that have antifungal activity similar to terbinafine. Approximately 70% of the administered dose is eliminated in the urine. In adult patients with renal impairment (creatinine clearance $\leq$ 50 mL/min) or hepatic cirrhosis, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers [see *Warnings and Precautions (5.3)*].

12.4 Microbiology

Terbinafine, an allylamine antifungal, inhibits biosynthesis of ergosterol, an essential component of fungal cell membrane, via inhibition of squalene epoxidase enzyme. This results in fungal cell death primarily due to the increased membrane permeability mediated by the accumulation of high concentrations of squalene but not due to ergosterol deficiency. Depending on the concentration of the drug and the fungal species tested *in vitro*, terbinafine may be fungicidal. However, the clinical significance of *in vitro* data is unknown.

Lamisil Oral Granules has been studied in tinea capitis [see *Clinical Studies (14)*].

13 NONCLINICAL TOXICOLOGY

13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In a 28-month oral carcinogenicity study in rats, an increase in the incidence of liver tumors was observed in males at the highest dose tested, 69 mg/kg/day (2x the MRHD based on AUC comparisons of the parent terbinafine); however, even though dose-limiting toxicity was not achieved at the highest tested dose, higher doses were not tested.

The results of a variety of *in vitro* (mutations in *E. coli* and *S. 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. Oral reproduction studies in rats at doses up to 300 mg/kg/day (approximately 12x the MRHD based on BSA comparisons) did not reveal any specific effects on fertility or other reproductive parameters. Intravaginal application of terbinafine hydrochloride at 150 mg/day in pregnant rabbits did not increase the incidence of abortions or premature deliveries nor affect fetal parameters.

13.2 ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY

A wide range of *in vivo* studies in mice, rats, dogs, and monkeys, and *in vitro* studies using rat, monkey, and human hepatocytes suggest that peroxisome proliferation in the liver is a rat-specific finding. However, other effects, including increased liver weights and APTT, occurred in dogs and monkeys at doses giving C_{ss} trough levels of the parent terbinafine 2-3x those seen in humans at the MRHD. Higher doses were not tested.

In a 52 week oral toxicology study conducted in juvenile maturing dogs, increased heart and liver weights were noted in males and signs of CNS disturbance including 3 cases of single episodes of seizures were noted in females at the highest dose tested, 100 mg/kg/day [19X (males) and 10X (females) the MRHD based on AUC comparisons of the parent terbinafine]. No treatment related

findings were noted at 30 mg/kg/day [1.6X (males) and 1.9X (females) the MRHD based on AUC comparisons of the parent terbinafine] in this study.

14 CLINICAL STUDIES

Two randomized, multinational trials were conducted to investigate the safety and efficacy of Lamisil (terbinafine hydrochloride) Oral Granules in the treatment of subjects 4 to 12 years old with tinea capitis. Lamisil Oral Granules was dosed based on body weight. Griseofulvin dosed at 10-20 mg/kg was used as a comparator. Subjects were dosed for 6 weeks and followed for an additional 4 weeks.

The two trials enrolled 50% of subjects from the U.S. Additionally, among those with positive cultures, 65% and 54% of infections were due to *T. tonsurans*, and 19% and 17% due to *M. canis* in Studies 1 and 2, respectively.

The primary efficacy endpoint was the proportion of subjects with complete cure (negative KOH, negative culture and absence of clinical signs of infection) at week 10. Table 3 below lists the efficacy results for Studies 1 and 2 overall and according to the dermatophyte species (*T. tonsurans*, *M. canis*, or Other).

Table 3. Primary Efficacy Results by Dermatophyte Species

	Study 1		Study 2	
	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
All Dermatophytes	(N=411)	(N=197)	(N=441)	(N=237)
Complete Cure	190 (46.2%)	67 (34.0%)	194 (44.0%)	103 (43.5%)
<i>T. tonsurans</i>	(N= 264)	(N= 131)	(N= 243)	(N= 126)
Complete Cure	148 (56.1%)	45 (34.4%)	116 (47.7%)	46 (36.5%)
<i>M. canis</i>	(N= 80)	(N= 37)	(N= 72)	(N= 45)
Complete Cure	19 (23.8%)	13 (35.1%)	22 (30.6%)	23 (51.1%)
Other*	(N= 67)	(N= 29)	(N= 126)	(N=66)
Complete Cure	23 (34.2%)	9 (31.0%)	56 (44.4%)	34 (51.5%)

* *T. violaceum*, *M. audouinii*, *T. mentagrophytes*, *T. rubrum*, *M. gypseum*, and *M. vanbreuseghemii*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamisil (terbinafine hydrochloride) Oral Granules 125 mg and 187.5 mg

Lamisil Oral Granules is supplied in cartons containing 14 laminated aluminum packets. Each packet contains approximately either 30 or 45 off-white to yellowish, round, biconvex, film-coated granules, corresponding to a single total dose of 125 mg or 187.5 mg (terbinafine base equivalent) per packet.

125 mg per packet

Carton of 14 packets.....NDC 0078-0499-58

Pack of 3 cartons each containing 14 packets (42 packets).....NDC 0078-0499-59

187.5 mg per packet

Carton of 14 packets.....NDC 0078-0500-58

Pack of 3 cartons each containing 14 packets (42 packets).....NDC 0078-0500-59

Storage conditions of Lamisil Oral Granules 125 mg and 187.5 mg: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.5)

17.1 Instructions for Use

Patients should be informed that Lamisil Oral Granules should be taken once a day with food. Patients should sprinkle the contents of each packet on a spoonful of pudding or other soft, non-acidic food such as mashed potatoes and swallow the entire spoonful; applesauce or fruit-based foods should not be used. The combination of food and granules should be swallowed without chewing. If two packets are required with each dose, the patient may either sprinkle the content of both packets on one spoonful of non-acidic food, or the sprinkle the contents of both packets on two spoonfuls of non-acidic food as directed above.

17.2 Monitoring Laboratory Tests

Pre-treatment serum transaminases (ALT and AST) tests are advised for all patients taking Lamisil Oral Granules.

17.3 Hepatotoxicity

Patients prescribed Lamisil Oral Granules and/or their guardian should be warned to report immediately to their physician any symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain, jaundice, dark urine or pale stools.

17.4 Skin Rash

Patients should be informed that if a progressive skin rash occurs, treatment with Lamisil Oral Granules should be discontinued.

Appears This Way
On Original

17.5 FDA-Approved Patient Labeling

PATIENT INFORMATION

Lamisil (terbinafine hydrochloride) Oral Granules

Read the Patient Information that comes with Lamisil Oral Granules before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your specific scalp condition or treatment.

What is Lamisil Oral Granules?

Lamisil Oral Granules is indicated for the treatment of tinea capitis in patients 4 years of age and older.

What is tinea capitis?

Tinea capitis is a dermatophyte infection of the scalp hair follicles which occurs primarily in children.

How long will it take Lamisil Oral Granules to work?

Treatment time for tinea capitis is 6 weeks.

How are Lamisil Oral Granules taken?

Your physician will prescribe dosing based upon your body weight. One to two packets should be taken each day with a soft non-acidic food, (see patient instructions below). For best results the patient should take the complete course of prescribed medicine. If two packets are required with each dose, you may either sprinkle the content of both packets on one spoonful of non-acidic food, or sprinkle the contents of both packets on two spoonfuls of non-acidic food as directed below.

Patient instructions:

1. Hold packet with cut line on top.
2. Shake packet gently to settle contents.
3. Tear packet open along cut line, or use scissors to cut across line.
4. Carefully pour entire contents of packet onto a spoonful of a soft food, such as pudding or other soft, non-acidic food such as mashed potatoes (do not use applesauce or a fruit-based food).
5. Make sure that no granules remain in the packet.
6. Swallow combination of food and granules without chewing.

Who should not use Lamisil Oral Granules?

Lamisil Oral Granules should not be taken by anyone allergic to any of its ingredients. Also, Lamisil Oral Granules should not be taken by anyone who has problems with his or her liver or kidneys, or by pregnant or nursing women, unless directed by your doctor. Lamisil Oral Granules has the potential to interact with other drugs, including some commonly prescribed antidepressants, beta-blockers, and antiarrhythmics. Tell your doctor if you are taking any of these or any other prescription or over-the-counter medications.

What are the possible side effects of Lamisil Oral Granules?

Serious side effects on the liver, including death and liver transplant, have occurred in people taking terbinafine. Because of the potential for liver damage, people with liver disease should not take Lamisil Oral Granules.

How do I know if my liver is healthy?

It is recommended that your doctor conduct a blood test to check your liver before prescribing Lamisil Oral Granules. You should watch for symptoms of liver problems while taking Lamisil Oral Granules. If you experience persistent nausea, loss of appetite, fatigue, vomiting, right upper abdominal pain, yellowing of skin, dark urine or pale stools while taking Lamisil Oral Granules, stop taking Lamisil Oral Granules immediately and call your doctor right away.

Are there other possible side effects?

Lamisil Oral Granules may cause some side effects in some people. Some commonly reported side effects in clinical studies were headache, fever, vomiting, upper respiratory tract infection, abdominal pain, diarrhea, nausea, and itching. Because some people have developed serious skin conditions while taking oral Lamisil, stop taking Lamisil Oral Granules and tell your doctor if you develop a rash. Also, tell your doctor if you experience any other side effects.

What else should I know before taking Lamisil Oral Granules?

Decreases in white blood cell count have been reported. If you have problems with your immune system, your doctor may need to monitor your white blood cell count carefully if you take Lamisil Oral Granules for more than 6 weeks. In some cases, Lamisil Oral Granules therapy may need to be discontinued.

Prolonged taste disturbances have been reported, in some instances severe enough to result in decreased food intake leading to significant and unwanted weight loss. Tell your doctor if you notice these symptoms.

How should I store Lamisil Oral Granules?

Store Lamisil Oral Granules at 59–86°F and keep this and all other medications away from children.

Lamisil Oral Granules were prescribed only for you; do NOT share the medication with anyone else.

Manufactured by:

Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
T2007-66/T2007-67

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On Original

NDC 0078-0499-62		Rx only	Lot & Exp. Area
LAMISIL[®]			
(terbinafine hydrochloride)			
Oral Granules			
125 mg			
terbinafine base equivalent per packet			
Mfd by: Novartis Pharma Stein AG		©Novartis	
Stein, Switzerland		XXXXXXX	

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	Refer to Patient instructions on back of carton prior to use.	

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Appears This Way
On Original

NDC 0078-0500-62		Rx only
LAMISIL[®] (terbinafine hydrochloride)		Lot & Exp. Area
Oral Granules		
187.5 mg terbinafine base equivalent per packet		
Mfd by: Novartis Pharma Stein AG ©Novartis Stein, Switzerland XXXXXXXX		

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	Refer to Patient instructions on back of carton prior to use.	

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