



NDA 20-539/S-012

Novartis Pharmaceuticals Corporation
Attention: Cheryl Elder, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Elder:

Please refer to your supplemental new drug application dated July 18, 2003, received July 21, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LAMISIL[®] (terbinafine hydrochloride tablets) Tablets, 250 mg.

We also acknowledge receipt of your submission dated July 31, 2003.

This supplemental new drug application provides for labeling revisions to the Drug Interactions Sub-section of the PRECAUTIONS Section and to the ADVERSE REACTIONS section.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-539/S-012." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81)

If you have any questions, please call Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stanka Kukich
1/21/04 05:10:40 PM
signing for Dr. Jonathan Wilkin, Division Director



LAMISIL[®]
(terbinafine hydrochloride tablets)

Tablets

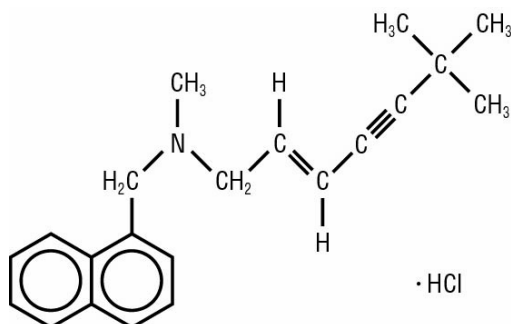
Rx only

Prescribing Information

DESCRIPTION

LAMISIL[®] (terbinafine hydrochloride tablets) Tablets 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. The empirical formula C₂₁H₂₆ClN 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 tablet contains:

Active Ingredients: terbinafine hydrochloride (equivalent to 250 mg base)

Inactive Ingredients: colloidal silicon dioxide, NF; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of LAMISIL[®] (terbinafine hydrochloride tablets) Tablets as a result of first-pass metabolism is approximately 40%. Peak plasma concentrations of 1 µg/mL appear within 2 h after a single 250 mg

terbinafine of less than 20% is observed when LAMISIL[®] is administered with food. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been reported. In patients with renal impairment (creatinine clearance $\leq 50\text{mL}/\text{min}$) or hepatic cirrhosis, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers. No effect of gender on the blood levels of terbinafine was detected in clinical trials. In plasma, terbinafine is >99% bound to plasma proteins and there are no specific binding sites. At steady-state, in comparison to a single dose, the peak concentration of terbinafine is 25% higher and plasma AUC increases by a factor of 2.5; the increase in plasma AUC is consistent with an effective half-life of ~36 hours. Terbinafine is distributed to the sebum and skin. A terminal half-life of 200-400 h may represent the slow elimination of terbinafine from tissues such as skin and adipose. Prior to excretion, terbinafine is extensively metabolized. No metabolites have been identified that have antifungal activity similar to terbinafine. Approximately 70% of the administered dose is eliminated in the urine.

Microbiology

Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine hydrochloride is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. *In vitro*, mammalian squalene epoxidase is only inhibited at higher (4000 fold) concentrations than is needed for inhibition of the dermatophyte enzyme. Depending on the concentration of the drug and the fungal species test *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 microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

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:

Candida albicans

Epidermophyton floccosum

Scopulariopsis brevicaulis

CLINICAL STUDIES

The efficacy of LAMISIL[®] (terbinafine hydrochloride tablets) Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials.

Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).

In a second toenail study of dermatophytic onychomycosis, in which non-dermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the non-

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