TERBINAFINE HYDROCHLORIDE- terbinafine hydrochloride tablet
DirectRX

TERBINAFINE HYDROCHLORIDE

INDICATIONS & USAGE SECTION

Terbinafine tablets, USP are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium).

Prior to initiating treatment, appropriate nail specimens for laboratory testing [potassium hydroxide (KOH) preparation, fungal culture, or nail biopsy] should be obtained to confirm the diagnosis of onychomycosis.

DOSAGE & ADMINISTRATION SECTION

Fingernail onychomycosis: One 250 mg tablet once daily for 6 weeks.

Toenail onychomycosis: One 250 mg tablet once daily for 12 weeks.

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.

DOSAGE FORMS & STRENGTHS SECTION

Tablet, 250 mg white, circular biconvex tablets debossed with "C134" on one side and plain on the other side.

CONTRAINDICATIONS SECTION

Terbinafine tablets, USP are contraindicated in individuals with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis.

WARNINGS AND PRECAUTIONS SECTION

- 5.1 Hepatotoxicity
  Cases of liver failure, some leading to liver transplant or death, have occurred with the use of terbinafine tablets in individuals with and without preexisting liver disease.
  In the majority of liver cases reported in association with use of terbinafine tablets, 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 terbinafine tablets should be discontinued if biochemical or clinical evidence of liver injury develops.
  Terbinafine tablets are not recommended for patients with chronic or active liver disease. Before prescribing terbinafine tablets, liver function tests should be performed since hepatotoxicity may occur in patients with and without pre-existing liver disease. Periodic monitoring of liver function tests is recommended. Terbinafine hydrochloride should be immediately discontinued in case of elevation of liver function tests. Patients prescribed terbinafine tablets 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 oral terbinafine, and the patient's liver function should be immediately evaluated.
  5.2 Taste Disturbance Including Loss of Taste
  Taste disturbance, including taste loss, has been reported with the use of terbinafine tablets. It can be severe enough to result in decreased food intake, weight loss, anxiety, and depressive symptoms.

Taste disturbance may resolve within several weeks after discontinuation of treatment, but may be prolonged (greater than 1 year), or may be permanent. If symptoms of a taste disturbance occur, terbinafine tablets should be discontinued.

5.3 Smell Disturbance Including Loss of Smell

Smell disturbance, including loss of smell, has been reported with the use of terbinafine tablets. Smell disturbance may resolve after discontinuation of treatment, but may be prolonged (greater than 1 year), or may be permanent. If symptoms of a smell disturbance occur, terbinafine tablets should be discontinued.

5.4 Depressive Symptoms

Depressive symptoms have occurred during postmarketing use of terbinafine tablets. Prescribers should be alert to the development of depressive symptoms, and patients should be instructed to report depressive symptoms to their physician.

5.5 Hematologic Effects

Transient decreases in absolute lymphocyte counts (ALCs) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 terbinafine hydrochloride-treated subjects (1.7%) and 3/137 placebo-treated subjects (2.2%) had decreases in ALC to below 1000/mm3 on 2 or more occasions. In patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts if treatment continues for more than 6 weeks. Cases of severe neutropenia have been reported. These were reversible upon discontinuation of terbinafine tablets, 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 ≤1000 cells/mm3, terbinafine tablets should be discontinued and supportive management started.

5.6 Serious Skin/Hypersensitivity Reactions

There have been postmarketing reports of serious skin/hypersensitivity reactions [e.g., Stevens - Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and bullous dermatitis, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome]. Manifestations of DRESS syndrome may include cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more organ complications such as hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. If progressive skin rash or signs/symptoms of the above drug reactions occur, treatment with terbinafine tablets should be discontinued.

5.7 Lupus Erythematosus

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

5.8 Laboratory Monitoring

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

ADVERSE REACTIONS SECTION

- 6.1 Clinical Trials 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.

  The most frequently reported adverse events observed in the 3 US/Canadian placebo-controlled trials are listed in the table below. The adverse events reported encompass gastrointestinal symptoms (including diarrhea, dyspepsia, and abdominal pain), liver test abnormalities, rashes, urticaria, pruritus, and taste disturbances. Changes in the ocular lens and retina have been reported following the use of terbinafine tablets in controlled trials. The clinical significance of these changes is unknown. In general, the adverse events were mild, transient, and did not lead to discontinuation from study participation.

Adverse

	Adverse Event		Discontinuation	
	Terbinafine tablets (%) n = 465	Placebo (%) n = 137	Terbinafine tablets (%) n = 465	Placebo (%) n = 137
Headache	12.9	9.5	0.2	0.0
Gastrointestinal Symptoms:				
Diarrhea	5.6	2.9	0.6	0.0
Dyspepsia	4.3	2.9	0.4	0.0
Abdominal Pain	2.4	1.5	0.4	0.0
Nausea	2.6	2.9	0.2	0.0
Flatulence	2.2	2.2	0.0	0.0
Dermatological Symptoms:				
Rash	5.6	2.2	0.9	0.7
Pruritus	2.8	1.5	0.2	0.0
Urticaria	1.1	0.0	0.0	0.0
Liver Enzyme Abnormalities *	3.3	1.4	0.2	0.0
Taste Disturbance	2.8	0.7	0.2	0.0
Visual Disturbance	1.1	1.5	0.9	0.0

*Liver enzyme abnormalities ≥ 2× the upper limit of normal range.

6.2 Postmarketing Experience

The following adverse events have been identified during postapproval use of terbinafine tablets. 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.

Blood and lymphatic system disorders: Pancytopenia, agranulocytosis, severe neutropenia, thrombocytopenia, anemia [see Warnings and Precautions (5.5)]

Immune system disorders: Serious hypersensitivity reactions e.g., angioedema and allergic reactions (including anaphylaxis), precipitation and exacerbation of cutaneous and systemic lupus erythematosus [see Warnings and Precautions (5.7)], serum sickness-like reaction

Psychiatric disorders: Anxiety and depressive symptoms independent of taste disturbance have been reported with use of terbinafine tablets. In some cases, depressive symptoms have been reported to subside with discontinuance of therapy and to recur with reinstitution of therapy [see Warnings and Precautions (5.4)]

Nervous system disorders: Cases of taste disturbance, including taste loss, have been reported with the use of terbinafine tablets. It can be severe enough to result in decreased food intake, weight loss, anxiety, and depressive symptoms. Cases of smell disturbance, including smell loss, have been reported with the use of terbinafine tablets [see Warnings and Precautions (5.2 and 5.3)]. Cases of paresthesia and hypoesthesia have been reported with the use of terbinafine tablets.

Eye disorders: Visual field defects, reduced visual acuity

Ear and labyrinth disorders: Hearing impairment, vertigo, tinnitus

Vascular disorders: Vasculitis

Gastrointestinal disorders: Pancreatitis, vomiting

Hepatobiliary disorders: Cases of liver failure some leading to liver transplant or death [see

Warnings and Precautions (5.1)], idiosyncratic and symptomatic hepatic injury. Cases of hepatitis, cholestasis, and increased hepatic enzymes [see Warnings and Precautions (5.1)] have been seen with the use of terbinafine tablets.

Skin and subcutaneous tissue disorders: Serious skin reactions [e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and bullous dermatitis, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome] [see Warnings and Precautions (5.6)], acute generalized exanthematous pustulosis, psoriasiform eruptions or exacerbation of psoriasis, photosensitivity reactions, hair loss

Musculoskeletal and connective tissue disorders: Rhabdomyolysis, arthralgia, myalgia

General disorders and administration site conditions: Malaise, fatigue, influenza-like illness, pyrexia

Investigations: Altered prothrombin time (prolongation and reduction) in patients concomitantly treated with warfarin and increased blood creatine phosphokinase have been reported.

DRUG INTERACTIONS SECTION

- 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 terbinafine tablets 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 Cmax and a 5-fold increase in area under the curve (AUC). In this study, these effects were shown to persist at the last observation at 4 weeks after discontinuation of terbinafine tablets. In studies in healthy subjects characterized as extensive metabolizers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increases the dextromethorphan/ dextrorphan metabolite ratio in urine by 16-to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolizers to poor metabolizer status.

In vitro studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin, cyclosporine, cisapride and fluvastatin. 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, cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline was not considered to be clinically significant. Coadministration of a single dose of fluconazole (100 mg) with a single dose of terbinafine resulted in a 52% and 69% increase in terbinafine Cmax and AUC, respectively. Fluconazole is an inhibitor of CYP2C9 and CYP3A 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 (Cmax and AUC) of terbinafine when concomitantly administered.

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 terbinafine 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 terbinafine tablets was conducted. An increase of less than 20% of the AUC of terbinafine was observed when terbinafine tablets were administered with food. Terbinafine tablets can be taken with or without food.

USE IN SPECIFIC POPULATIONS SECTION

- 8.1 Pregnancy

  Pregnancy Category B

  There are 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 terbinafine tablets not be initiated during pregnancy.

  Oral reproduction studies have been performed in rabbits and rats at doses up to 300 mg/kg/day [12× to 23× 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.

  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 terbinafine tablets is not recommended in women who are nursing.

  8.4 Pediatric Use

  The safety and efficacy of terbinafine tablets have not been established in pediatric patients with onychomycosis.

  8.5 Geriatric Use

  Clinical studies of terbinafine tablets did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

  8.6 Renal Impairment

  In patients with renal impairment (creatinine clearance less than or equal to 50 mL/min) the use of terbinafine tablets has not been adequately studied.

OVERDOSAGE SECTION

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

DESCRIPTION SECTION

- Terbinafine tablets, USP contain the synthetic allylamine antifungal compound terbinafine hydrochloride USP.

  Chemically, terbinafine hydrochloride is (E)-N-(6, 6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The empirical formula C21H26CIN with a molecular weight of 327.90, and the following structural formula:

  Terbinafine hydrochloride, USP 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, USP (equivalent to 250 mg base)

  Inactive Ingredients: colloidal silicon dioxide NF, hypromellose USP, magnesium stearate NF, microcrystalline cellulose NF, and sodium starch glycolate NF.

CLINICAL PHARMACOLOGY SECTION

- 12.1 Mechanism of Action

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

  12.2 Pharmacodynamics

  The pharmacodynamics of terbinafine tablets is unknown.

  12.3 Pharmacokinetics

  Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of terbinafine tablets as a result of first-pass metabolism is approximately 40%. Peak plasma concentrations of 1 µg/mL appear within 2 hours after a single 250 mg dose; the AUC is approximately 4.56 µg.h/mL. An increase in the AUC of terbinafine of less than 20% is observed when terbinafine tablets are administered with food.

  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 hours may represent the slow elimination of terbinafine from tissues such as skin and adipose. Prior to excretion, terbinafine is extensively metabolized by at least 7 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 patients with renal impairment (creatinine clearance ≤50 mL/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. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been reported.

  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 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:

  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

NONCLINICAL TOXICOLOGY SECTION

- 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 (2× 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 12× 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 Css trough levels of the parent terbinafine 2–3× those seen in humans at the MRHD. Higher doses were not tested.

CLINICAL STUDIES SECTION

The efficacy of terbinafine tablets in the treatment of onychomycosis is illustrated by the response of subjects with toenail and/or fingernail infections who participated in 3 US/Canadian placebo-controlled clinical trials.

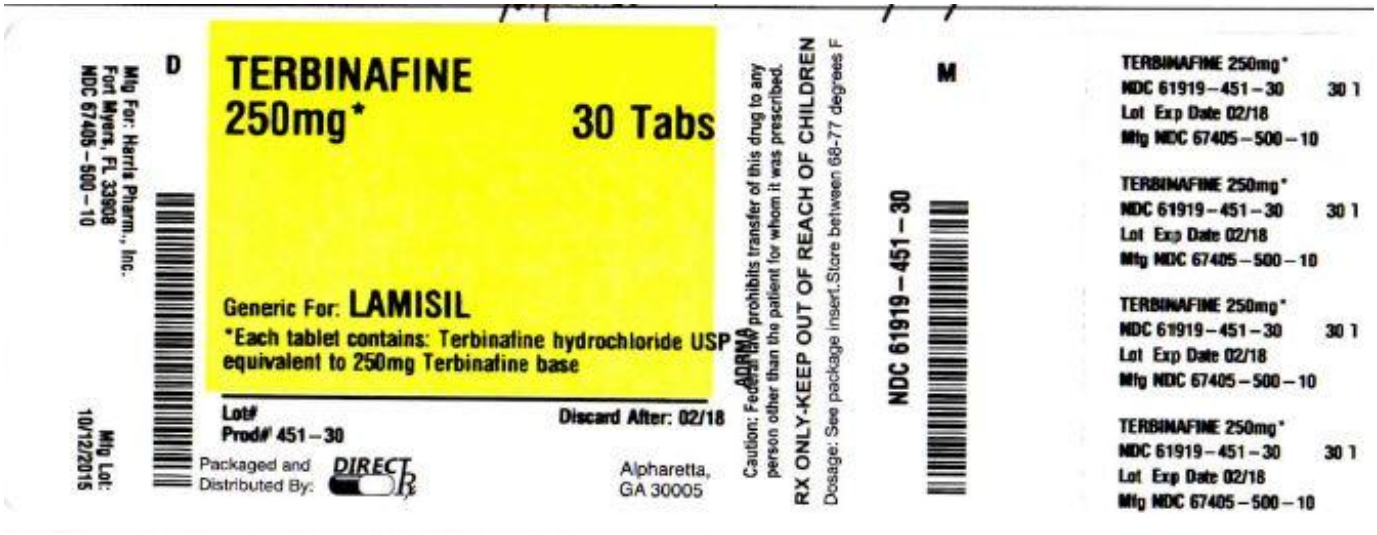
Results of the first toenail trial, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of subjects. Fifty-nine percent (59%) of subjects experienced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

In a second toenail trial of dermatophytic onychomycosis, in which nondermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the nondermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

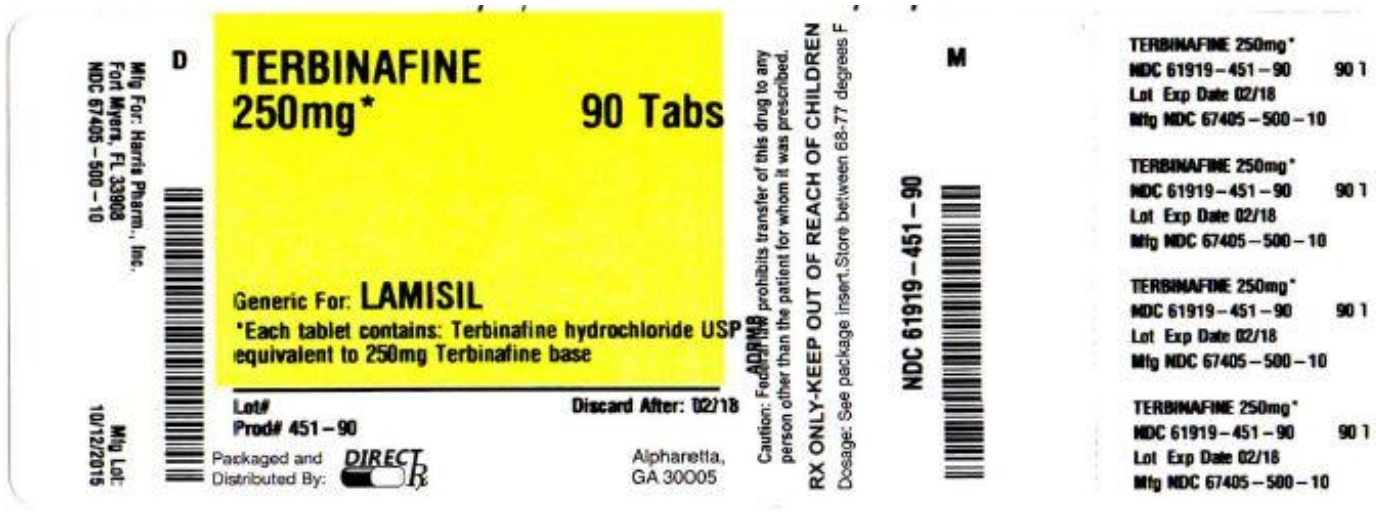
Results of the fingernail trial, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of subjects, effective treatment in 75% of the subjects, and mycological cure plus clinical cure in 59% of the subjects.

The mean time to overall success was approximately 10 months for the first toenail trial and 4 months for the fingernail trial. In the first toenail trial, for subjects evaluated at least 6 months after achieving clinical cure and at least 1 year after completing therapy with terbinafine tablets, the clinical relapse rate was approximately 15%.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



TERBINAFINE HYDROCHLORIDE

terbinafine hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-451(NDC:67405-500)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TERBINAFINE HYDROCHLORIDE (UNII: 012C11ZU6G) (TERBINAFINE - UNII:G7RIW8S0XP)	TERBINAFINE HYDROCHLORIDE	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	

Product Characteristics

Color	white	**Score**	no score
Shape	ROUND (circular biconvex)	**Size**	11mm
Flavor		**Imprint Code**	C134
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-451-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2015	
2	NDC:61919-451-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077137	01/01/2015	

Labeler - DirectRX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DirectRX		079254320	repack(61919-451)

Revised: 5/2020 DirectRX