

**TERBINAFINE HYDROCHLORIDE- terbinafine hydrochloride tablet**  
**Wockhardt USA LLC.**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use TERBINAFINE HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for TERBINAFINE HYDROCHLORIDE TABLETS.**

**TERBINAFINE hydrochloride tablets, for oral use**  
**Initial U.S. Approval: 1992**

----- **RECENT MAJOR CHANGES** -----

Dosage and Administration: Assessment Prior to Initiation (2.1) 8/2016  
Contraindications (4) 8/2016  
Warnings and Precautions: Hepatotoxicity (5.1) 8/2016  
Warnings and Precautions: Thrombotic Microangiopathy (5.8) 1/2017

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

Terbinafine hydrochloride tablets are an allylamine antifungal indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium). (1) (1)

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

- Prior to administering, evaluate patients for evidence of chronic or active liver disease. (2.1)
- Fingernail onychomycosis: One 250 mg tablet, once daily for 6 weeks. (2.2)
- Toenail onychomycosis: One 250 mg tablet, once daily for 12 weeks. (2.2)

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

Tablet, 250 mg (3) (3)

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

- History of allergic reaction to oral terbinafine because of the risk of anaphylaxis. (4)
- Chronic or active liver disease. (4)

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

- Liver failure, sometimes leading to liver transplant or death, has occurred with the use of oral terbinafine. Obtain pretreatment serum transaminases. Prior to initiating treatment and periodically during therapy, assess liver function tests. Discontinue terbinafine hydrochloride tablets if liver injury develops. (5.1)
- Taste disturbance, including taste loss, has been reported with the use of terbinafine hydrochloride tablets. Taste disturbance can be severe, may be prolonged, or may be permanent. Discontinue terbinafine hydrochloride tablets if taste disturbance occurs. (5.2)
- Smell disturbance, including loss of smell, has been reported with the use of terbinafine hydrochloride tablets. Smell disturbance may be prolonged, or may be permanent. Discontinue terbinafine hydrochloride tablets if smell disturbance occurs. (5.3)
- Depressive symptoms have been reported with terbinafine use. Prescribers should be alert to the development of depressive symptoms. (5.4)
- Severe neutropenia has been reported. If the neutrophil count is less than or equal to 1000 cells/mm<sup>3</sup>, terbinafine hydrochloride tablets should be discontinued. (5.5)
- Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, bullous dermatitis, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with oral terbinafine use. If signs or symptoms of drug reaction occur, treatment with terbinafine hydrochloride tablets should be discontinued. (5.6)

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

Common (greater than 2% of patients treated with terbinafine hydrochloride tablets) reported adverse events include headache, diarrhea, rash, dyspepsia, liver enzyme abnormalities, pruritus, taste disturbance, nausea, abdominal pain, and flatulence. (6.1) (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Wockhardt USA LLC. at 1-800-346-6854 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). (6)**

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

Terbinafine is an inhibitor of CYP450 2D6 isozyme and has an effect on metabolism of desipramine. Drug interactions have also been noted with cimetidine, fluconazole, cyclosporine, rifampin, and caffeine. (7.1) (7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

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## 1 INDICATIONS AND USAGE

Terbinafine hydrochloride tablets 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Assessment Prior to Initiation

Before administering terbinafine hydrochloride tablets, evaluate patients for evidence of chronic or active liver disease [see *Contraindications (4) and Warnings and Precautions (5.1)*].

### 2.2 Dosage

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.

## 3 DOSAGE FORMS AND STRENGTHS

Terbinafine hydrochloride tablets 250 mg, supplied as white circular, bi-convex, bevelled tablets embossed with 'W' on one side and '743' on other side.

## 4 CONTRAINDICATIONS

Terbinafine hydrochloride tablets are contraindicated in patients with:

- History of allergic reaction to oral terbinafine because of the risk of anaphylaxis [see *Adverse Reactions (6.2)* ]
- Chronic or active liver disease [see *Warnings and Precautions (5.1)* ]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hepatotoxicity

Terbinafine hydrochloride tablets are contraindicated for patients with chronic or active liver disease. Before prescribing terbinafine hydrochloride tablets, perform liver function tests because hepatotoxicity may occur in patients with and without preexisting liver disease. Cases of liver failure, some leading to liver transplant or death, have occurred with the use of terbinafine hydrochloride tablets in individuals with and without preexisting liver disease.

In the majority of liver cases reported in association with use of terbinafine hydrochloride 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. Periodic monitoring of liver function tests is recommended. Discontinue terbinafine hydrochloride tablets if biochemical or clinical evidence of liver injury develops.

Warn patients prescribed terbinafine hydrochloride tablets and/or their caregivers to report immediately to their healthcare providers any symptoms or signs of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine, or pale stools. Advise patients with these symptoms

to discontinue taking oral terbinafine, and immediately evaluate the patient's liver function.

## **5.2 Taste Disturbance Including Loss of Taste**

Taste disturbance, including taste loss, has been reported with the use of terbinafine hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride tablets should be discontinued.

## **5.4 Depressive Symptoms**

Depressive symptoms have occurred during postmarketing use of terbinafine hydrochloride 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 subjects receiving terbinafine hydrochloride tablets (1.7%) and 3/137 subjects receiving placebo (2.2%) had decreases in ALC to below 1000/mm<sup>3</sup> 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 hydrochloride 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 less than or equal to 1000 cells/mm<sup>3</sup>, terbinafine hydrochloride 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, 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 hydrochloride 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 hydrochloride tablets. Terbinafine hydrochloride tablets should be discontinued in patients with clinical signs and symptoms suggestive of lupus erythematosus.

## **5.8 Thrombotic Microangiopathy**

Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, some fatal, have been reported with terbinafine. Discontinue terbinafine if clinical symptoms and laboratory findings consistent with TMA occur. The findings of unexplained

thrombocytopenia and anemia should prompt further evaluation and consideration of diagnosis of TMA.

## 6 ADVERSE REACTIONS

### 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 hydrochloride 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 Event                               |                   | Discontinuation                             |                   |
|-----------------------------|---|-------------------|---|-------------------|
|                             | Terbinafine hydrochloride tablets (%) n=465 | Placebo (%) n=137 | Terbinafine hydrochloride 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 greater than or equal to 2x the upper limit of normal range.

### 6.2 Postmarketing Experience

The following adverse events have been identified during post-approval use of terbinafine hydrochloride 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, thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic

purpura and hemolytic uremic syndrome [see *Warnings and Precautions (5.5, 5.8)*].

*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 hydrochloride tablets. In some cases, depressive symptoms have been reported to subside with discontinuance of therapy and to recur with reinstatement 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 hydrochloride 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 hydrochloride tablets [see *Warnings and Precautions (5.2, 5.3)*]. Cases of paresthesia and hypoesthesia have been reported with the use of terbinafine hydrochloride 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 hydrochloride tablets.

*Skin and subcutaneous tissue disorders:* Serious skin reactions [e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, 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

## **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 terbinafine hydrochloride 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  $C_{max}$  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 hydrochloride tablets. In studies in healthy subjects characterized as extensive metabolizers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increases the dextromethorphan/ dextrophan 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  $C_{max}$  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 ( $C_{max}$  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 hydrochloride 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 hydrochloride tablets was conducted. An increase of less than 20% of the AUC of terbinafine was observed when terbinafine hydrochloride tablets were administered with food. Terbinafine hydrochloride tablets can be taken with or without food.

## **8 USE IN SPECIFIC POPULATIONS**

### **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 hydrochloride tablets not be initiated during pregnancy.

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.

### **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 hydrochloride tablets is not recommended in women who are nursing.

### **8.4 Pediatric Use**

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

### **8.5 Geriatric Use**

Clinical studies of terbinafine hydrochloride 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 hydrochloride tablets has not been adequately studied.

## 8.7 Hepatic Impairment

Terbinafine hydrochloride tablets are contraindicated for patients with chronic or active liver disease [see *Contraindications (4) and Warnings and Precautions (5.1)*]. Cases of liver failure, some leading to liver transplant or death, have occurred with the use of terbinafine hydrochloride tablets in individuals with and without preexisting liver disease. The severity of hepatic events and/or their outcome may be worse in patients with active or chronic liver disease.

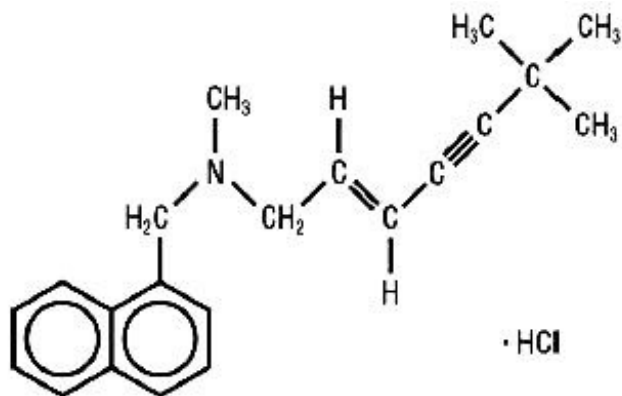
## 10 OVERDOSAGE

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.

## 11 DESCRIPTION

Terbinafine hydrochloride 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  $C_{21}H_{26}ClN$  with a molecular weight of 327.90, and the following structural formula:



Terbinafine hydrochloride is a white to off-white 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:* microcrystalline cellulose, NF; hypromellose 6 cps, USP; sodium starch glycolate, NF; colloidal silicon dioxide, NF; magnesium stearate, 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 terbinafine hydrochloride tablets is unknown.

### 12.3 Pharmacokinetics

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

In plasma, terbinafine is greater than 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 to 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 less than or equal to 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*

## 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.

## 14 CLINICAL STUDIES

The efficacy of terbinafine hydrochloride 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 greater than 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 hydrochloride tablets, the clinical relapse rate was approximately 15%.



Terbinafine (ter-BIN-ah-fin)

hydrochloride tablets

### **What is the most important information I should know about terbinafine hydrochloride tablets?**

Terbinafine hydrochloride tablets may cause serious side effects, including:

- **Liver problems that can lead to the need for a liver transplant or death** . This can happen in people who have liver problems and in people who have never had liver problems. Tell your doctor right away if you get any of these symptoms of liver problems:

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|                 |   |
|-----------------|---|
| o nausea        | o upper right stomach-area (abdomen) pain   |
| o poor appetite | o yellowing of your skin or eyes (jaundice) |
| o tiredness     | o dark (tea-colored) urine                  |
| o vomiting      | o pale or light colored stools              |

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Your doctor should do a blood test to check you for liver problems before you start treatment with terbinafine hydrochloride tablets. Your doctor may also check you for liver problems during treatment, and tell you to stop taking terbinafine hydrochloride tablets if you develop liver problems.

### **What are terbinafine hydrochloride tablets?**

Terbinafine hydrochloride tablet is a prescription medicine used to treat fungal infections of the fingernails and toenails (onychomycosis).

Your doctor should do tests to check you for fungal infection of your nails before you start terbinafine hydrochloride tablets.

It is not known if terbinafine hydrochloride tablets are safe and effective in children for the treatment of onychomycosis.

### **Who should not take terbinafine hydrochloride tablets?**

#### **Do not take terbinafine hydrochloride tablets if you:**

- have had a severe allergic reaction to terbinafine hydrochloride when taken by mouth.
- have had liver disease for a long time (chronic) or have active liver disease.

### **What should I tell my doctor before taking terbinafine hydrochloride tablets?**

#### **Before taking terbinafine hydrochloride tablets, tell your doctor about all of your medical conditions, including if you:**

- have or had liver problems
- have a weakened immune system (immunocompromised)
- have lupus (an autoimmune disease)
- are pregnant or plan to become pregnant. It is not known if terbinafine hydrochloride tablets will harm your unborn baby. You should not start taking terbinafine hydrochloride tablets during pregnancy.
- are breastfeeding or plan to breastfeed. Terbinafine hydrochloride passes into your breast milk and may harm your baby. You should not breastfeed while taking terbinafine hydrochloride tablets. Talk to your doctor about the best way to feed your baby if you take terbinafine hydrochloride tablets.

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Terbinafine hydrochloride tablets may affect the way other medicines work and other medicines may affect how terbinafine hydrochloride tablets work.

### **How should I take terbinafine hydrochloride tablets?**

- Take terbinafine hydrochloride tablets exactly as your doctor tells you to take it.

- Terbinafine hydrochloride tablets comes as a tablet that you take by mouth.
- **Terbinafine hydrochloride tablets are usually taken:**
  - o **1 time each day for 6 weeks to treat fungal infections of your fingernail, or**
  - o **1 time each day for 12 weeks to treat fungal infections of your toenail**
- Terbinafine hydrochloride tablets can be taken with or without food.
- If you miss a dose of terbinafine hydrochloride tablets, take it as soon as you remember. If it is less than 4 hours before your next dose, skip the missed dose. Just take the next dose at your regular time.
- If you take too many terbinafine hydrochloride tablets, call your doctor. You may have the following symptoms:

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|                               |            |             |
|-------------------------------|------------|-------------|
| o nausea                      | o rash     | o vomiting  |
| o stomach-area (abdomen) pain | o headache | o dizziness |
| o frequent urination          |            |             |

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### **What should I avoid while taking terbinafine hydrochloride tablets?**

Avoid sunlight. Terbinafine hydrochloride tablets can make your skin sensitive to the sun and the light from sunlamps and tanning beds. You can get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight. Talk to your doctor if you get sunburn.

### **What are the possible side effects of terbinafine hydrochloride tablets?**

**Terbinafine hydrochloride tablets may cause serious side effects, including:**

- See "**What is the most important information I should know about terbinafine hydrochloride tablets?**"
- **Change in your sense of taste or loss of taste** is common with terbinafine hydrochloride tablets, but can also be severe. This may improve within several weeks after you stop taking terbinafine hydrochloride tablets, but may last for a long time or may become permanent. Tell your doctor if you develop any of the following:

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|  |               |
|--|---------------|
| o change in your sense of taste or loss of taste   | o weight loss |
| o poor appetite  | o anxiousness |
| o change in your mood or depressive symptoms. See the list of depressive symptoms below. |               |

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- **Change in your sense of smell or loss of smell** may happen with terbinafine hydrochloride tablets. This may improve after you stop taking terbinafine hydrochloride tablets, but may last for a long time or may become permanent. Tell your doctor if you have a change in your sense of smell or loss of smell.
- **Depressive symptoms. Tell your doctor right away if you develop any of these signs or symptoms :**

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|                           |  |
|---------------------------|--|
| o feel sad or worthless   | o loss of energy or interest in daily activities |
| o change in sleep pattern | o restlessness                                   |
| o mood changes            |  |

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- **Low white blood cell count.** Terbinafine hydrochloride tablets may decrease your white blood cell count, especially neutrophils. You may have a higher risk of getting an infection when your white blood cell count is low.

- **Serious skin or allergic reactions, which may include problems with some of your body organs . Tell your doctor right away or get emergency medical help if you get any of these symptoms:**

- o skin rash
- o hives
- o sores in your mouth, or your skin blisters and peels
- o swelling of your face, eyes, lips, tongue or throat
- o trouble swallowing or breathing
- o fever
- o swollen lymph glands

Also tell your doctor about any new symptoms, such as cough, chest pain, fast heartbeat, or blood in your urine.

- **New or worsening lupus.** Stop taking terbinafine hydrochloride tablets and tell your doctor if you get any of the following:

- o a skin rash that gets worse (progresses), is scaly, red, shows scarring, or loss of skin color
- o unusual sensitivity to the sun that can cause a rash

- **Blood clotting problems.** When taking terbinafine hydrochloride tablets, you may develop a blood clotting problem. Tell your doctor, if you get any unexplained bleeding or bruising.

The most common side effects of terbinafine hydrochloride tablets include:

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|            |                                 |                               |
|------------|---------------------------------|-------------------------------|
| o headache | o upset stomach                 | o nausea                      |
| o diarrhea | o abnormal liver function tests | o stomach-area (abdomen) pain |
| o rash     | o itching                       | o gas                         |

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These are not all of the possible side effects of terbinafine hydrochloride tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store terbinafine hydrochloride tablets?**

- Store terbinafine hydrochloride tablets between 20°-25°C (68°-77°F) (See USP Controlled Room Temperature).
- Keep terbinafine hydrochloride tablets in a tightly closed container and keep out of the light.

#### **Keep terbinafine hydrochloride tablets and all medicines out of the reach of children.**

#### **General information about the safe and effective use of terbinafine hydrochloride tablets.**

Medicines are sometimes prescribed for purposes other than those listed in Medication Guide. Do not use terbinafine hydrochloride tablets for a condition for which it was not prescribed. Do not give terbinafine hydrochloride tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about terbinafine hydrochloride tablets that is written for health professionals.

#### **What are the ingredients in terbinafine hydrochloride tablets?**

Active ingredient: terbinafine hydrochloride

Inactive ingredients: microcrystalline cellulose, NF; hypromellose 6 cps, USP; sodium starch

glycolate, NF; colloidal silicon dioxide, NF; magnesium stearate, NF.

This Medication Guide has been approved by the U.S. Food and Drug Administration

**Manufactured by:**

Wockhardt Limited

H-14/2, M.I.D.C. Area, Waluj,

Aurangabad, Maharashtra,

India.

**Distributed by:**

Wockhardt USA LLC.

20 Waterview Blvd.

Parsippany, NJ 07054

USA.

Rev.201117

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

DRUG: Terbinafine Hydrochloride

GENERIC: Terbinafine Hydrochloride

DOSAGE: Tablets

ADMINISTRATION: Oral

NDC: 64679-743-01

STRENGTH: 250 mg

COLOR: White

SHAPE: Round (Bi-convex, beveled)

SCORE: no score

SIZE: 11 mm

IMPRINT: W;743

QTY: 30 Tablets

\*Each tablet contains: Terbinafine hydrochloride equivalent to 250 mg of terbinafine base.

NDC 64679-743-01

Usual adult dosage: See package insert for dosage information.

Store between 20°-25°C (68°-77°F)  
(See USP Controlled Room Temperature)  
in a tight container.  
Protect from light.

Manufactured by:  
Wockhardt Limited,  
H-14/2, M.I.D.C. Area,  
Waluj, Aurangabad,  
Maharashtra, India.

Distributed by:  
Wockhardt USA LLC,  
20 Waterview Blvd.  
Parsippany, NJ 07054  
USA.

# Terbinafine hydrochloride Tablets

**250 mg\***

PHARMACIST: Dispense the enclosed  
Medication Guide to each patient.

30 Tablets

Rx only



Lot:  
Exp.:

Rev.201117

## TERBINAFINE HYDROCHLORIDE

terbinafine hydrochloride tablet

### Product Information

|                         |                         |                    |               |
|-------------------------|-------------------------|--------------------|---------------|
| Product Type            | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:64679-743 |
| Route of Administration | ORAL                    |                    |               |

### Active Ingredient/Active Moiety

| Ingredient Name  | Basis of Strength | Strength |
|--|-------------------|----------|
| TERBINAFINE HYDROCHLORIDE (UNII: 012C11ZU6G) (TERBINAFINE - UNII:G7RIW8S0XP) | TERBINAFINE       | 250 mg   |

### Inactive Ingredients

| Ingredient Name  | Strength |
|--|----------|
| CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)           |          |
| HYPROMELLOSE 2910 (6 MPAS) (UNII: 0WZ8WG20P6)            |          |
| MAGNESIUM STEARATE (UNII: 70097M6I30)                    |          |
| SILICON DIOXIDE (UNII: ETJ7Z6XBU4)                       |          |
| SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2) |          |

### Product Characteristics

|          |                             |              |          |
|----------|-----------------------------|--------------|----------|
| Color    | WHITE                       | Score        | no score |
| Shape    | ROUND (bi-convex, bevelled) | Size         | 11mm     |
| Flavor   |                             | Imprint Code | W;743    |
| Contains |                             |              |          |

### Packaging

| # | Item Code        | Package Description                                | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:64679-743-01 | 30 in 1 BOTTLE; Type 0: Not a Combination Product  | 07/02/2007           |                    |
| 2 | NDC:64679-743-03 | 100 in 1 BOTTLE; Type 0: Not a Combination Product | 07/02/2007           |                    |



|   |                  |   |            |  |
|---|------------------|---|------------|--|
| 3 | NDC:64679-743-02 | 1000 in 1 BOTTLE; Type 0: Not a Combination Product     | 07/02/2007 |  |
| 4 | NDC:64679-743-04 | 10 in 1 CARTON  | 07/02/2007 |  |
| 4 |                  | 10 in 1 BLISTER PACK; Type 0: Not a Combination Product |            |  |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA               | ANDA078229                               | 07/02/2007           |                    |

**Labeler** - Wockhardt USA LLC. (170508365)

**Registrant** - Wockhardt Limited (650069115)

## Establishment

| Name              | Address | ID/FEI    | Business Operations   |
|-------------------|---------|-----------|---|
| Wockhardt Limited |         | 676257570 | ANALYSIS(64679-743) , MANUFACTURE(64679-743) , LABEL(64679-743) , PACK(64679-743) |

Revised: 11/2019

Wockhardt USA LLC.