For the use only of a Registered Medical Practitioners or a Hospital or a Laboratory

Terbinafine

TERBIKEM TABLET

1. NAME OF THE MEDICINAL PRODUCT

Terbinafine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Terbinafine hydrochloride……..250mg

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Terbinafine hydrochloride Tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes.

4.2 Posology and Method of Administration

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.

4.3 Contraindications

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

4.4 Special Warnings and Special Precautions for Use

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 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.

Taste Disturbance Including Loss of Taste

Taste disturbance, including taste loss, has been reported with the use of TerbinafineTablets. 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.

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.

Depressive Symptoms

Depressive symptoms have occurred during post marketing 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.

Hematologic Effects

Transient decreases in absolute lymphocyte counts (ALCs) have been observed in controlled clinical trials.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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.

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.

4.6 Fertility, Pregnancy and Lactation

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.

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 Terbinfine Tablets is not recommended in women who are nursing.

Pediatric Use

The safety and efficacy of Terbinafine Tablets have not been established in pediatric patients with onychomycosis.

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.

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.

4.7 Undesirable Effects

General

In general, terbinafine side effects have been mild and transient. However, the drug has been associated with serious life threatening events such as hepatic failure, anaphylaxis, and severe neutropenia.

Nervous system: Very common (10% or more): Headache (12.9%)
Frequency not reported: Dizziness, insomnia
Taste disturbance (including taste loss; some cases severe enough to cause decreased food intake, weight loss, anxiety, depressive symptoms), smell disturbance (including loss of smell), paresthesia, hypoesthesia, tinnitus, hearing impairment, vertigo

Gastrointestinal: Common (1% to 10%): Diarrhea (5.6%), dyspepsia (4.3%), taste disturbance (2.8%), nausea (2.6%), abdominal pain (2.4%), flatulence (2.2%)
Rare (less than 0.1%): Severe sialadenitis (at least 1 case)
Frequency not reported: Mild to moderate gastrointestinal discomfort, gastritis, gastric fullness, nausea and vomiting, taste alteration (rarely accompanied by discoloration of the tongue and/or disturbance in the sense of smell), hypogeusia, ageusia, metallic taste
Vomiting, pancreatitis

Patients with hiatal hernia or gastric duodenal ulcer disease may be more likely to experience mild to moderate gastrointestinal discomfort, diarrhea, dyspepsia, nausea and vomiting, gastritis, gastric fullness, and flatulence.

Taste disturbances were typically noticed 5 to 8 weeks after starting therapy and returned to normal 2 to 5 weeks after stopping the medication. The taste alteration has been rarely accompanied by a discoloration of the tongue and/or a disturbance in the sense of smell.

Dermatologic: Common (1% to 10%): Rash (5.6%), pruritus (2.8%), urticaria (1.1%)
Rare (less than 0.1%): Reversible alopecia areata of the scalp, pustular psoriasis, acrodermatitis continua of Hallopeau (at least 1 case)
Frequency not reported: Erythema multiforme
Serious skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, bullous dermatitis, drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome), psoriasiform eruptions or exacerbation of psoriasis, acute generalized exanthematous pustulosis, hair loss, photosensitivity reactions, precipitation and exacerbation of cutaneous and systemic lupus erythematosus

Hepatic: Common (1% to 10%): Liver enzyme abnormalities (2 times ULN or greater; 3.3%)Rare (less than 0.1%): Terbinafine-induced autoimmune hepatitis (at least 1 case)
Frequency not reported: Transient elevations in serum liver enzymes, development of idiosyncratic and symptomatic hepatobiliary dysfunction
Idiosyncratic and symptomatic hepatic injury, cases of liver failure (some leading to death or liver transplantation), hepatitis, cholestasis, increased hepatic enzymes

Hematologic

Frequency not reported: Leukopenia, lymphopenia
Pancytopenia, anemia, thrombocytopenia, agranulocytosis, severe neutropenia, altered prothrombin time (prolonged and reduced) with concomitant warfarin

Ocular: Common (1% to 10%): Visual disturbance (1.1%)
Frequency not reported: Changes in ocular lens and retina, dyschromatopsia, photopsia
Reduced visual acuity, visual field defect

Changes in the ocular lens and retina have been reported; however, the clinical significance is unknown.

Dyschromatopsia, whereby the patient reported a greenish hue in her vision, and photopsia have occurred in a patient after 3 weeks of therapy. This problem resolved within 1 week of discontinuing the drug.

Metabolic: Frequency not reported: Hypoglycemia, hypotriglyceridemia

Renal: Rare (less than 0.1%): Renal function test impairment

Genitourinary: Rare (less than 0.1%): Hematuria, transient erectile dysfunction in male patients (extremely rare)

Hypersensitivity

Rare (less than 0.1%): Anaphylaxis, hypersensitivity reactions
Serious hypersensitivity reactions (e.g., angioedema, allergic reactions [including anaphylaxis]), serum sickness-like reaction

Musculoskeletal

Arthralgia, myalgia, rhabdomyolysis, increased blood creatine phosphokinase

Cardiovascular: Vasculitis

Other: Malaise, fatigue, influenza-like illness, pyrexia

Psychiatric: Anxiety (independent of taste disturbance), depressive symptoms (independent of taste disturbance)

4.8 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Terbinafine is an allylamine antifungal. The pharmacodynamics of Terbinafine Tablets is unknown.

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.

5.2 Pharmacokinetic Properties

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.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life: 36 months

6.2 Special Precautions for Storage: Store in a cool dry place protected from light

6.3 Nature and contents of container: 2* 7 Tablets

Marketed By:

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Lower Parel; Mumbai,
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