Dermafine®

Terbinafine

FORMS AND PRESENTATION
Dermafine®: Tablets: Box of 15.
COMPOSITION:
Dermafine®: Each tablet contains: Terbinafine Hydrochloride eq. to Terbinafine 250 mg.
Excipients: microcrystalline cellulose, hydroxy propyl cellulose, magnesium stearate, colloidal anhydrous silica, crospovidone, croscarmellose sodium.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations, Terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity versus yeasts is fungicidal or fungistatic depending on the species.
Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system. When given orally, the drug concentrates in skin at levels associated with fungicidal activity.
Pharmacokinetic Properties
A single oral dose of 250mg Terbinafine results in mean peak plasma concentrations of 0.97µg/ml within 2 hours after administration. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. Terbinafine binds strongly to plasma proteins. It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum.
Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum rich skins. There is also evidence that Terbinafine is distributed into the nail plate within the first few weeks of commencing therapy. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The elimination half-life is 17 hours. There is no evidence of accumulation.
No age-dependent changes in pharmacokinetics have been observed but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of Terbinafine.
The bioavailability of Terbinafine is unaffected by food.
Preclinical safety data
In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.
In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumors was observed in males at the highest dosage level of 69mg/kg a day. The changes which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in the carcinogenicity study in mice, dogs or monkeys.
During high-dose studies in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic effect level 50mg/kg). These irregularities were associated with the presence of a Terbinafine metabolite in ocular tissue and disappeared after drug discontinuation. They were not associated with histological changes.
A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.
No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.
INDICATIONS
Fungal infections of the skin and nails caused by Trichophyton (eg. *T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum.*
Dermafine® is indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection.
Dermafine® is indicated in the treatment of onychomycosis.
CONTRAINDICATIONS
Hypersensitivity to Terbinafine or to any of the excipients.
PRECAUTIONS
Liver Function
Terbinafine tablets are not recommended for patients with chronic or active liver disease. Before prescribing Terbinafine tablets, any pre-existing liver disease should be assessed.
Hepatotoxicity may occur in patients with and without pre-existing liver disease.
Very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with Terbinafine tablets. In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Terbinafine tablets was uncertain.
Patients prescribed Terbinafine tablets should be instructed to report immediately any signs or symptoms suggestive of liver dysfunction such as pruritus, unexplained persistent nausea, anorexia or tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine, or pale stools. Patients with these symptoms should discontinue taking oral Terbinafine and the patient's liver function should be immediately evaluated.
Dermatological effects
Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) have been very rarely reported in patients taking Terbinafine tablets. If progressive skin rash occurs, Terbinafine tablets treatment should be discontinued.
Hematological effects
Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with Terbinafine tablets. Etiology of any blood dyscrasias that occur in patients treated with Terbinafine tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Terbinafine tablets.
Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of Terbinafine may be reduced by about 50%.
Terbinafine should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported.
Renal function
In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 µmol/L) the use of Terbinafine tablets has not been adequately studied, and therefore, is not recommended.
PREGNANCY AND LACTATION
Foetal toxicity and fertility studies in animals suggest no adverse effects.
There is no clinical experience with Terbinafine in pregnant women; therefore, unless the potential benefits outweigh any potential risks, Terbinafine should not be administered during pregnancy.
Terbinafine is excreted in breast milk and therefore mothers should not receive Terbinafine treatment whilst breast-feeding.
DRUG INTERACTIONS
Effect of other medicinal products on Terbinafine
The plasma clearance of Terbinafine may be accelerated by drugs which induce metabolism and may be inhibited by drugs which inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of Terbinafine may need to be adjusted accordingly.
Cimetidine decreased the clearance of Terbinafine by 30%.
Rifampicin increased the clearance of Terbinafine by 100%.
Effect of Terbinafine on other medicinal products
Studies undertaken *in vitro* and in healthy volunteers suggest that Terbinafine shows negligible potential to inhibit or induce the clearance of drugs that are metabolized via other cytochrome P450 enzymes (e.g.

tolbutamine, terfenadine, triazolam, oral contraceptives) with exception of those metabolized through CYP2D6.
Terbinafine does not interfere with the clearance of antipyrine or digoxin.
Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking Terbinafine concomitantly with oral contraceptives.
Terbinafine may increase the effect or plasma concentration of the following medicinal products:
Caffeine – Terbinafine decreased the clearance of caffeine administered intravenously by 21%.
Compounds predominantly metabolized by CYP2D6 – *In vitro* and *in vivo* studies have shown that Terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for patients receiving compounds predominantly metabolized by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B.
Terbinafine decreased the clearance of desipramine by 82%.
Terbinafine may decrease the effect or plasma concentration of the following medicinal products:
Terbinafine increased the clearance of ciclosporin by 15%.
Rare cases of changes in INR and/or prothrombin time have been reported in patients receiving Terbinafine concomitantly with warfarin.

ADVERSE EFFECTS

Adverse effects are generally mild to moderate, and transient. The following adverse effects have been observed in the clinical trials or during post-marketing experience.
Adverse effects are ranked under headings of frequency, using the following convention:
Very common (≥1/10); Common (≥1/100, < 1/10); Uncommon (≥ 1/1,000, <1/100); Rare (≥1/10,000, < 1/1,000); Very rare (< 1/10,000), including isolated reports.
Blood and lymphatic system disorders: Very rare: neutropenia, agranulocytosis, thrombocytopenia. Not known: pancytopenia.
Immune system disorders: Very rare: anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.
Psychiatric disorders: Very rare: psychiatric disturbances (such as depression and anxiety).
Nervous system disorders: Common: headache. Uncommon: taste disturbances, including taste loss, which usually recover slowly after discontinuation of the drug. Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss. Rare: paraesthesia, hypoaesthesia, dizziness.
Ear and labyrinth disorders: Very rare: vertigo.
Gastrointestinal disorders: Very common: gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhea).
Hepatobiliary disorders: Rare: cases of serious hepatic dysfunction, including jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with Terbinafine should be discontinued. Very rare cases of serious liver failure have been reported (some with a fatal outcome, or requiring liver transplant). In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Terbinafine was uncertain.
Skin and subcutaneous tissue disorders: Very common: non-serious forms of skin reactions (rash, urticaria). Very rare: serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, and photosensitivity). If progressive skin rash occurs, Terbinafine treatment should be discontinued. Not known: psoriasiform eruptions or exacerbation of psoriasis, serious skin reactions (e.g. acute generalized exanthematous pustulosis).
Musculoskeletal and connective tissue disorders: Very common: musculoskeletal reactions (arthralgia, myalgia).
General disorders: Rare: malaise. Not known: fatigue.

DOSAGE AND ADMINISTRATION

Adults
250mg tablet once daily.
The duration of treatment varies according to the indication and the severity of the infection.
Skin infections
Likely durations of treatment are as follows:
Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks
Tinea corporis: 4 weeks
Tinea cruris: 2 to 4 weeks
Onychomycosis
The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.
Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.
Additional information on special population
Liver impairment
Dermafine® tablets are not recommended for patients with chronic or active liver disease.
Renal impairment
The use of Dermafine® tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population.
Children
A review of safety experience with oral Terbinafine in children, which includes 314 patients involved in the UK Terbinafine Post Marketing Surveillance study, has shown that the adverse effect profile in children is similar to that seen in adults. No evidence of any new, unusual or more severe reactions to those seen in the adult population have been noted. However, as data is still limited, its use is not recommended.
Elderly
There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group.

OVERDOSAGE

Few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. The recommended treatment of overdosage consists in eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: February 2014.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Medicament: keep out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

PI072/2

Benta SAL
Dbayeh- Lebanon

Prepared by: Nisrine Wehbeh **Date:** Feb 2014
Product Name: Dermafine **Type:** Package insert
Die Cut N°: N/A **Die Cut Dimension:** 160*200
Version N°: 1 **Market:** Lebanon-export countries
Specification: **Code:** PI072
Reason for Revision: Modification in storage condition

Delivered to Logistic Department:
Name: **Date:**

Color Shade number:
Black

Checked & Approved by:
RA : **Date:**
Production: **Date:**
Marketing: **Date:**
Quality Assurance: **Date:**