TERBINAFORCE 250

(Terbinafine Tablets USP 250 mg)

1. NAME OF MEDICINAL PRODUCT

TERBINAFORCE 250 : (Terbinafine Tablets USP 250 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TERBINAFORCE 250 : Each uncoated tablet contains: Terbinafine Hydrochloride USP equivalent to Terbinafine 250 mg

Excipients: For a full list of excipients, please refer Section 6.1.

3. PHARMACEUTICAL FORMS

TERBINAFORCE 250 : White to off-white coloured, round, biconvex, uncoated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indicated for the treatment of fungal infections of the skin and nails caused by *Trichophyton (T.rubrum, T.mentagrophytes, T.verrucosum, T.violaceum)*, *Microsporum canis* and *Epidermophyton floccosum*.

1. Indicated for 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.

2. Indicated in the treatment of onychomycosis

4.2 Posology and method of administration

Adults: 250mg once daily

The duration of treatment varies according to the indication and severity of the infection.

Skin Infections

Likely duration of treatment are as follows:

Tinea pedis (interdigital, plantar/moccoasin type):	2 to 6 weeks
Tinea corporis:	4 weeks
Tinea cruris:	2 to 4 weeks

Onychomycosis

For most patients the duration of treatment is between 6 weeks and 3 months although treatment periods of less than 3 months can be anticipated in younger patients or those with fingernail infections or toenail infections other than the big toe. 3 months is usually sufficient in the treatment of toenail infections although some patients may require 6 months treatment or longer. Poor nail outgrowth during the first weeks of treatment may indicate those patients where longer therapy is required. The complete resolution of signs and symptoms of infection may not occur until several weeks after mycological cure.

Additional information on special population

Liver impairment

Terbinafine Tablets USP 250 mg tablets are contraindicated for patients with chronic or active hepatic disease (see section 4.3 Contraindications and 4.4. Special warnings and precautions for use).

Renal impairment

The use of Terbinafine Tablets USP 250 mg tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Children

Due to limited data, use is not recommended.

Elderly

There is no evidence to suggest that elderly patients (aged 65 years or above) 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 (see Precautions).

Method of administration:

The tablets are taken orally with water. They should preferably be taken at the same time each day and can be taken on an empty stomach or after a meal.

4.3 Contraindications

Known hypersensitivity to terbinafine or to any of the excipients listed in section 6.1.

Chronic or active hepatic disease.

4.4 Special Warnings and Precautions for use

Liver Function

Terbinafine Tablets USP 250 mg tablets are contraindicated for patients with chronic or active hepatic disease. Before prescribing Terbinafine Tablets USP 250 mg, a liver function test should be performed and any pre-existing liver disease should be assessed.

Hepatotoxicity may occur in patients with and without pre-existing liver disease therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended. Terbinafine Tablets USP 250 mg should be immediately discontinued in case of elevation of liver function test.

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. (see section 4.3 Contraindications and 4.8 Undesirable effects).

Patients prescribed Terbinafine Tablets USP 250 mg should be instructed to report immediately any signs or symptoms suggestive of liver dysfunction such as pruritus, unexplained persistent nausea, decreased appetite, anorexia, jaundice, vomiting, fatigue, right upper abdominal pain, 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, drug rash with eosinophilia and systemic symptoms) have been very rarely reported. If progressive skin rash occurs, Terbinafine Tablets USP 250 mg tablets treatment should be discontinued.

Terbinafine Tablets USP 250 mg tablets should be used with caution in patients with pre-existing psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

Haematological effects

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported. Aetiology of any blood dyscrasias that occur in patients treated with Terbinafine Tablets USP 250 mg tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Terbinafine Tablets USP 250 mg tablets.

Renal function

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) the use of terbinafine tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).

Other

Terbinafine Tablets USP 250 mg tablets should be used with caution in patients with lupus erythematosus as very rare cases of lupus erythematosus have been reported.

4.5 Interaction with other medicinal products and other forms of interaction

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 Terbinaforce 250 tablets may need to be adjusted accordingly.

The following medicinal products may increase the effect or plasma concentration of terbinafine:

Cimetidine decreased the clearance of terbinafine by 30%.

Fluconazole increased the Cmax and AUC of terbinafine by 52% and 69% respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

The following medicinal products may decrease the effect or plasma concentration of terbinafine:

Rifampicin increased the clearance of terbinafine by 100%.

Effect of terbinafine on other medicinal products

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 metabolised 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 metabolised 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, especially if they also have a narrow therapeutic window.

Terbinafine decreased the clearance of desipramine by 82%.

Terbinafine may convert extensive CYP2D6 metabolisers (genotype) to poor metaboliser (phenotype) status.

Information on other drug concomitantly used with Terbinaforce 250 tablets resulting in no or negligible interactions

Terbinafine shows negligible potential to inhibit or induce the clearance of most drugs that are metabolised via other cytochrome P450 enzymes (e.g. tolbutamine, terfenadine, triazolam, oral contraceptives) with exception of those metabolised through CYP2D6.

Terbinafine does not interfere with the clearance of antipyrine or digoxin.

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further there was no clinically relevant interaction between terbinafine and the potential comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking terbinafine tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

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.

4.6 Pregnancy and Lactation

Pregnancy

Foetal toxicity and fertility studies in animals suggest no adverse effect. Since clinical experience in pregnant women is very limited, terbinafine tablets should not be used during pregnancy unless clinical conditions of the woman requires treatment with oral terbinafine and the potential benefits for the mother outweigh any potential risks for the foetus.

Lactation

Terbinafine is excreted in breast milk and therefore mothers should not receive Terbinafine Tablets USP 250 mg tablets treatment whilst breast feeding.

Fertility

Foetal toxicity and fertility studies in animals suggest no adverse effects.

4.7 Effect on ability to drive and use machines

No studies on the effects of terbinafine tablets treatment on the ability to drive and use machines have been

performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable Effects

Side effects are generally mild to moderate and transient. Adverse reactions are ranked under headings of frequency using the following convention:

Very common: ≥ 1/10, Common: ≥ 1/100 to < 1/ 10, Uncommon: ≥ 1/ 1,000 to < 1/ 100, Rare: ≥ 1/10,000 to < 1/ 1,000, Very rare: < 1/10,000, Not known: frequency cannot be estimated from available data (including isolated reports)	
Blood and lymphatic system disorders	
Very rare	Neutropenia, agranulocytosis, thrombocytopenia.
Not known	Anaemia Pancytopenia
Immune system disorders	
Very rare	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.
Not known	Anaphylactic reaction, serum sickness like reaction.
Metabolism and nutrition disorders	
Very common	Decreased appetite
Psychiatric disorders	
Not known	Anxiety and depressive symptoms
Nervous system disorders	
Common	Headache
Uncommon	Dysgeusia* including ageusia* * Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.
Rare	Paraesthesia, hypoaesthesia, dizziness
Not known	Anosmia including permanent anosmia, hyposmia
Eye disorders	
Not known	Visual impairment, vision blurred, visual acuity reduced
Ear and labyrinth disorders	
Very rare	Vertigo
Not known	Hypoacusis, impaired hearing, tinnitus
Vascular disorders	
Not known	Vasculitis
Gastrointestinal disorders	
Very common	Gastrointestinal symptoms (feeling of fullness abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea).
Not known	Pancreatitis
Hepatobiliary disorders	
Rare	Cases of serious hepatic dysfunction, including hepatic failure, hepatic enzymes increased, jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with Terbinafine Tablets USP 250 mg tablets should be discontinued (see section 4.4).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 casual association with the intake of terbinafine tablets was uncertain.
Skin and subcutaneous tissue disorders	
Very common	Rash, urticaria.
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, toxic skin eruption, dermatitis exfoliative, dermatitis bullous. Photosensitivity reactions Alopecia If progressive skin rash occurs, Terbinafine Tablets USP 250 mg tablets treatment should be discontinued.
Not Known	Psoriasiform eruptions or exacerbation of psoriasis. Serious skin reactions [e.g. acute generalized exanthematous pustulosis (AGEP)]. Drug rash with eosinophilia and systemic symptoms.
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal reactions (arthralgia, myalgia).
Not Known	Rhabdomyolysis
General disorders	
Rare	Malaise
Not known	Fatigue Influenza-like illness, pyrexia
Investigations	
Uncommon	Weight decreased** **weight decreased secondary to dysgeusia
Not known	Blood creatine phosphokinase increased

4.9 Overdose

Few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. Recommended treatment for overdose consists of eliminating the active substance, primarily by the administration of activated charcoal to adsorb, and giving symptomatic supportive therapy if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Oral antifungal agent; ATC code: D01B A02

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 active substance concentrates in skin at levels associated with fungicidal activity.

Pharmacokinetics Properties

Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from terbinafine tablets as a result of first-pass metabolism is approximately 50%. A single oral dose of 250mg terbinafine resulted in mean peak plasma concentrations of 1.30µg/ml within 1.5 hours after administration. Plasma concentrations decline in a triphasic manner, with a terminal half-life of 16.5 days. At 28 days, when around 70% steady state levels have been achieved, peak concentrations of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3 when compared to single dose administration. From the increase in plasma AUC an effective half-life of ~30 hours can be calculated. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dose adjustments.

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.

Terbinafine is metabolised rapidly and extensively by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which is excreted predominantly in the urine.

No clinically-relevant 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.

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50 ml/min) or with pre-existing liver disease have shown that clearance of terbinafine tablets may be reduced by about 50%.

5.2 Pre-Clinical Safety Data

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 reproductive parameters were observed in studies in rats or rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxypropyl Methyl Cellulose (E-5), Colloidal Silicon Dioxide, Magnesium Stearate and Purified Water.

6.2 Incompatibilities

None known

6.3 Shelf Life

24 months from the date of manufacture.

6.4 Special Precautions for Storage

Do not store above 30ºC. Protect from light & moisture.

Keep all medicines out of the reach and sight of children.

6.5 Nature and Contents of Container:

10 tablets packed in Alu/Alu blister. 03 such blisters are packed in a carton along with package insert.

6.6 Special Precautions for Disposal

No special requirements.

7. DATE OF PUBLICATION OF INSERT

June'2019

Mankind

Manufactured by :
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