Terbiderm Forte Tablets

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Terbiderm Forte Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each contains:

Terbiderm(as Terbiderm HCL BP).....250mg

3. PHARMACEUTICAL FORM

Tablets for oral use only

White, round, biconvex, tablets having ATCO engraved on one side and bisect line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fungal infections of the skin and nails caused by Trichophyton (eg. T. rubrum, T.mentagrophytes, T. verrucosum, T. violaceum), Microsporumcanis and Epidermophytonfloccosum.

1. Oral Terbiderm Forte Tablets is indicated in the treatment of ringworm (tineacorporis, tineacruris and tineapedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection.

2. Oral Terbiderm Forte Tablets is indicated in the treatment of fungal infections of the nails (onychomycosis) which are caused by parasitic fungus that infects the skin (dermatophytes).

4.2 Posology and method of administration

Adults

250mg 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:

Tineapedis (interdigital, plantar/moccasin type): 2 to 6 weeks

Tineacorporis: 4 weeks

Tineacruris: 2 to 4 weeks

Dermatophyte infections of the nails (Onychomycosis)

Adult: 250 mg once daily for 6 weeks-3 months (occasionally longer in toenail infections).

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 populations

Liver impairment
Terbiderm Forte tablets are contraindicated for patients with chronic or active hepatic disease (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).
With oral use Manufacturer advises avoid—elimination reduced.

MONITORING REQUIREMENTS
With oral use Monitor hepatic function before and then every 4–6 weeks during treatment,if abnormalities in liver function tests.

Renal impairment
The use of Terbiderm Forte 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).
With oral use Use half normal dose if eGFR less than 50 mL/minute/1.73m2 and no suitable alternative available.

Children
A review of safety experience with oral Terbinafine in children, which includes 314 patients involved in the Terbinafine Post Marketing Surveillance study, has shown that the adverse event 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 (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 scored 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 of Terbiderm Forte tablets.
Chronic or active hepatic disease.

4.4 Special warnings and precautions for use

Liver Function
Terbiderm Forte tablets are contraindicated for patients with chronic or active hepatic disease. Before prescribing Terbiderm Forte tablets, 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. Terbiderm Forte tablets 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 Terbiderm Forte tablets. In the majority of liver failure cases the patients had serious underlying systemic conditions (see sections 4.3 Contraindications and 4.8 Undesirable effects).
Patients prescribed Terbiderm Forte tablets 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 in patients taking Terbiderm Forte tablets. If progressive skin rash occurs, Terbiderm Forte tablets treatment should be discontinued.
Terbiderm Forte 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 in patients treated with Terbiderm Forte tablets. Aetiology of any blood dyscrasias that occur in patients treated with Terbiderm Forte tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Terbiderm Forte 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 Terbiderm Forte tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).
Other
With oral use Autoimmune disease (risk of lupuserythematosus-like effect)
psoriasis (risk of exacerbation)

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 Terbiderm Forte 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 (see section 4.4).
Terbinafine decreased the clearance of desipramine by 82%.
In studies in healthy subjects characterized as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolisers (genotype) to poor metaboliser status (phenotype).

Information on other drug concomitantly used with Terbiderm Forte tablets resulting in no or negligible interactions.
Studies undertaken in vitro and in healthy volunteers suggest that terbinafine shows negligible potential to inhibit or induce the clearance of most drugs that are metabolized via other

cytochrome P450 enzymes (e.g. tolbutamine, terfenadine, triazolam, oral contraceptives) with exception of those metabolised through CYP2D6 (see below).

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 comedicationscotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking Terbiderm Forte 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 effects. Since clinical experience in pregnant women is very limited, terbinafine tablets should not be used during pregnancy unless clinical condition 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 Terbiderm Forte tablets treatment whilst breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Terbiderm Forte 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. The following adverse reactions have been observed in the clinical trials or during post-marketing experience.
Adverse reactions 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), Not known (frequency cannot be estimated from available data).

Common or very common
Abdominal Discomfort
Anorexia
Arthralgia
Diarrhoea Dyspepsia
Headache
Myalgia
Nausea
Rash
Urticaria
Uncommon
Taste disturbance
Rare
Cholestasis
Dizziness
Hepatitis .
Hypoaesthesia
Jaundice
Liver Toxicity
Malaise
Paraesthesia
Very Rare
Alopecia
Blood Disorders
Lupus Erythematosus-Like Effect
Neutropenia
Photosensitivity .
Serious Skin Reactions
Stevens-Johnson Syndrome .
Thrombocytopenia
Toxic Epidermal Necrolysis
Frequency not known
Disturbances In Smell
Exacerbation Of Psoriasis
Hearing Disturbances
Influenza-Like Symptoms .
Pancreatitis
Rhabdomyolysis
Vasculitis
Side-Effects, Further Information
Liver toxicity: Discontinue treatment if liver toxicity develops (including jaundice, cholestasis and hepatitis).
Serious skin reactions: Discontinue treatment in progressive skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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 drug concentrates in skin at levels associated with fungicidal activity.

5.2 Pharmacokinetic properties

Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from Terbiderm Forte 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 manor, 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 are 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 Terbiderm Forte may be reduced by about 50%.

5.3 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 tumours 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Hypromellose
Crospovidone
Colloidal Sillicon Dioxide
Magnesium Stearate
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

02 years.

6.4 Special precautions for storage

Keep out of the reach of children.
Protect from light & heat
Do not store above 30 ºC.

Do not use Terbiderm Forte tablets after the expiry date stated on the label/carton/bottle. The expiry date refers to the last day of that month.

6.5 Nature and contents of container

1 × 10’s tablets packed in Alu-Alublister , packed in a printed carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

ATCO Laboratories Limited
B-18, S.I.T.E.
Karachi-75700,
Pakistan

8. MARKETING AUTHORISATION NUMBER(S)

053367

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

December 16, 2008 / November 21, 2013