Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TERNAF 125 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 125 mg terbinafine as terbinafine hydrochloride.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

A white or almost white, round, scored, convex tablet, coded “TER 125” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of terbinafine sensitive fungal infections such as Tinea corporis, Tinea cruris and Tinea pedis (caused by Dermatophytes see 5.1 Pharmacodynamic properties) is considered appropriate due to the site, severity or extent of the infection.

The treatment of onychomycosis (terbinafine-sensitive fungal infection of the nails) caused by dermatophytes.

Consideration should be given to national recommendations on the appropriate use and prescription of antimicrobial agents.

4.2 Posology and method of administration

Adults
250 mg once daily

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

Skin infections
The likely durations of treatment for Tinea pedis, Tinea corporis and Tinea cruris are 2-4 weeks. For Tinea pedis (interdigital, plantar/moccasin-type): recommended treatment periods may be up to 6 weeks.

Onychomycosis
The duration of treatment (finger & toe nails) for most patients is between 6 weeks and 3 months. 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, and is only seen several months after stopping treatment, which is the time for outgrowth of a healthy nail.

Children and adolescents (< 18 years)
Experience of the use of terbinafine in children is limited and the use is not recommended.

Elderly people
No dose adjustments is necessary.

Impairment of liver or kidney function should be considered in this age group *(see section 4.4, Special warning and special precautions for use)*.

Hepatic impairment
Terbinafine is not recommended in severe hepatic impairment *(see section 4.4 Special warnings and special precautions for use).*

Renal impairment
Patients with impaired renal function (creatinine clearance less than 50 ml/min or serum creatinine of more than 300 µmol/l) should receive half the normal dose.

Method of administration
Oral use.

4.3 Contraindications

Hypersensitivity to terbinafine or to any of the excipients.
Severe hepatic impairment.
Severe renal impairment.

4.4 Special warnings and precautions for use

Hepatic impairment
Rarely, cases of cholestasis and hepatitis have been reported. This usually occurs within the first two months of the treatment.
Patients should be instructed immediately to report such symptoms.
If patients present with signs or symptoms suggestive of liver impairment such as pruritis, unexplained persistent nausea, anorexia, tiredness, jaundice, vomiting, fatigue, abdominal pain, dark urine or pale stools, hepatic origin should be verified and therapy with terbinafine should immediately be discontinued *(see section 4.8, Undesirable Effects).*

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50%. The therapeutic use of terbinafine in patients with chronic or active liver disease has not been studied in prospective clinical trials, and therefore cannot be recommended.

Renal impairment
Start the treatment with lower dosage due to modification of the product clearance *(see section, 4.2 Posology and method of administration)*.

Due to inhibition of CYP2D6 by terbinafine there is a risk of interaction with TCA's (tricyclic antidepressants), beta-blockers, SSRI's (selective serotonin reuptake inhibitors) and MAO-B inhibitors (monoamine oxidase inhibitors, type B) and patients should be monitored in case the co-medication has a small therapeutic window (see 4.5 Interaction with other medicinal products and other forms of interaction).

Patients should immediately discontinue the treatment and see a physician if the following symptoms occur: High fever or sore throat, pruritus, disseminated cutaneous disorders or cutaneous disorders with involvement of the mucosa *(see section 4.8, Undesirable Effects).*

Terbinafine should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported *(see section, 4.8 Undesirable Effects)*.

Orally administered terbinafine is not effective against Pityriasis versicolor and vaginal candidiasis.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that terbinafine inhibits CYP2D6 mediated metabolism. Patients who are receiving concomitant treatment with medicinal products that are primarily metabolised by this enzyme and having a narrow therapeutic index, such as metoprolol in chronic cardiac failure, antiarrhythmic agents (e.g. flecainide, propafenone) should be monitored if the therapeutic index of the concomitant medicinal product is small.

On the other hand, enzyme inducers (such as rifampicin) may increase the clearance of terbinafine. If coadministration of such agents is necessary, the dosage of terbinafine should be adjusted accordingly.

4.6 Pregnancy and lactation

Pregnancy:
Foetal toxicity and fertility studies in animals suggest no undesirable effects.

There is no adequate data from the use of terbinafine in pregnant women, therefore, terbinafine should not be administered during pregnancy unless clearly necessary.

Lactation:
Terbinafine is excreted in breast milk and therefore mothers should not receive treatment with terbinafine whilst breastfeeding.

4.7 Effects on ability to drive and use machines

Terbinafine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects of terbinafine are generally mild to moderate and transient.

	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				Neutropenia Thrombocytopenia Agranulocytosis *(See 4.4, Special warning and special precautions for use).*

	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)
Immune system disorders				Anaphylactoid reactions If a progressive rash occurs, the treatment with terbinafine should be discontinued. Lupus erythematosus or aggravation of the disease
Metabolism and nutrition disorders	Decreased appetite In isolated cases, considerable weight loss has been reported.			
Psychiatric disorders				Depression Anxiety
Nervous system disorders	Headache		Paraesthesia Hypaesthesia Dizziness Vertigo	
Gastrointestinal disorders	Dyspepsia Nausea Mild abdominal pain Diarrhoea Flatulence	Taste loss and taste disturbances in approximately 0.6% of patients treated with terbinafine. This usually resolves slowly on drug discontinuation.		
Hepato-biliary disorders			Hepatic impairment including cholestasis, jaundice and hepatitis. *(See 4.4, Special warning and special precautions for use).*	Prolonged hepatitis Severe hepatitis leading to liver transplantation or death

Skin and subcutaneous tissue disorders	Rash Urticaria		Photosensitivity Angioneurotic oedema Erythema multiforme If a progressive rash occurs, the treatment with terbinafine should be discontinued.	Alopecia Acute generalized exanthematous pustulosis Stevens Johnson syndrome Exacerbation of psoriasis Toxic epidermal necrolysis *(See 4.4, Special warning and special precautions for use).*
Musculoskeletal, connective tissue and bone disorders			Arthralgia Myalgia These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.	
General disorders and administration site conditions			Malaise Fatigue	

4.9 Overdose

A few cases of overdose (up to 5 g) 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

harmacotherapeutic group: Dermatologicals, antifungals for systemic use.

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.

When given orally, the drug concentrates in skin, hair and nails at levels associated with fungicidal activity. It is still present there 15 to 20 days after stopping treatment.

Terbinafine is used for the treatment of fungal infections of the skin and nails, which is caused by Trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum. The following table outlines the range of minimum inhibitory concentrations (MIC) against the dermatophytes.

Organism	MIC range (µg/ml)
Trichophyton rubrum	0.001 – 0.15
Trichophyton mentagrophytes	0.0001 – 0.05
Trichophyton verrucosum	0.001 – 0.006
Trichophyton violaceum	0.001 – 0.1
Microsporum canis	0.0001 – 0.1
Edidermorphyton fluccosum	0.001 – 0.05

Terbinafine exhibits poor efficacy against many yeasts of the Candida species.

Terbinafine tablets in contrast to locally administered terbinafine treatment, has no effect in the treatment of Pityriasis (Tinea) versicolor.

The enzyme squalene epoxidase is not linked to the cytochrome P450 system

5.2 Pharmacokinetic properties

A single dose of 250 mg of terbinafine results in peak plasma concentrations of 0.97 µg/ml within 2 hours of administration. The bioavailability of terbinafine may be somewhat affected by food, but the effect is of no clinical significance.

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the skin and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and parts of the skin rich in sebaceous glands. There is also evidence that terbinafine is distributed into the nail plate in a few weeks after commencing therapy.

Terbinafine is metabolised rapidly and extensively by at least seven CYP isoenzymes. It is mostly affected by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation produces metabolites which possess no antimycotic activity and which are predominantly excreted in the urine. The elimination half-life is 17 hours. No age-related changes in steady state plasma concentrations of terbinafine have been observed, but the elimination may be slower in patients with renal or hepatic impairment.

In patients with pre-existing mild to severe hepatic impairment, single dose pharmacokinetic studies have shown that the clearance of terbinafine can be reduced by 50%.

5.3 Preclinical safety data

In longterm studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100 mg/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 dose level of 69 mg/kg a day, at which systemic exposure was similar to clinical exposure. The mechanism of tumour development has not been established. The clinical relevance is unknown. The changes, which might 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 50 mg/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

Sodium Starch Glycolate (Type A)
Hypromellose
Colloidal Anhydrous Silica
Potato Starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Tablet container: Store in the original container in order to protect from light.

Blister: Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

Blister (Al/PVC) or polyethylene (HDPE) tablet containers and closures (tamper evident).

Pack sizes
10, 14, 16, 20, 28, 30, 42, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA 0711/071/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2005

10 DATE OF REVISION OF THE TEXT

April 2008