

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Terbinabine Medis 250mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg Terbinafine (as hydrochloride)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, scored on both sides, flat tablet marked "T" above and "1" below the score on one side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fungal infections of the skin and nails caused by *Trichophyton* (e.g. *T. rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*.

Oral terbinafine 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.

Onychomycosis (nail infections) caused by dermatophyte fungi.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

4.2 Posology and method of administration

Adults: 250mg once daily.

The bioavailability of terbinafine is not affected by food.

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.

Children: There is no experience with oral terbinafine in children and its use cannot therefore be recommended.

Use in the 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.

Method of administration: Via the oral route.

4.3 Contraindications

Hypersensitivity to terbinafine or any of the excipients.

4.4 Special warnings and precautions for use

Terbinafine is not recommended for patients with chronic or active liver disease. Before prescribing Terbinafine tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Patients prescribed Terbinafine tablets should be warned to report immediately any symptoms of unexplained 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.

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

In vitro and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with medicinal products predominantly metabolised by this enzyme, e.g. certain members of the following classes of medicinal product, tricyclic antidepressants (TCA's), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics class IC and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed, if the co-administered medicinal product has a narrow therapeutic window (see section 4.5, Interaction with Other Medicinal Products and Other Forms of Interaction).

Complete resolution of signs and symptoms of infection may not occur until several weeks after mycological cure.

Patients on terbinafine who develop a high fever or sore throat should be examined concerning a possible haematological reaction.

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 medicinal products, which induce metabolism and may be inhibited by medicinal products, which inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of Terbinafine 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 33%.

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:

According to the results from studies undertaken *in vitro* and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most medicinal products that are metabolised via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolised through CYP2D6 (see below).

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

Some cases of menstrual irregularities have been reported in patients taking Terbinafine concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

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

Caffeine: Terbinafine decreased the clearance of caffeine administered intravenously by 19%.

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 compounds predominantly metabolised by this enzyme, e.g. certain members of the following classes of medicinal product, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics class 1C and monoamine oxidase inhibitors (MAO-Is) Type B, and if they also have a narrow therapeutic window (see section 4.4, Special warnings and precautions for use).

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%.

4.6 Fertility, 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.

4.7 Effects on ability to drive and use machines

None.

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), including isolated reports.

Table 1:

General disorders	
Very rare	Fatigue
Blood and the lymphatic system disorders	
Very rare	Neutropenia, agranulocytosis, thrombocytopenia.
Immune system disorders	
Very rare	Anaphylactoid reactions (including angioedema, cutaneous and systemic lupus erythematosus).
Nervous system and psychiatric disorders	
Common Uncommon	Headache Taste disturbances, including taste loss, which usually recover within several weeks after discontinuation of the medicinal product [5]. Isolated cases of prolonged taste disturbances have been reported. A decrease of food intake leading to significant weight loss was observed in very few severe cases.
Hepato-biliary disorders	
Rare	Hepatobiliary dysfunction (primarily cholestatic in nature), including very rare cases of serious liver failure (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.
Gastrointestinal disorders	
Very common	Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).
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, acute generalized exanthematous pustulosis)*. Psoriasiform eruptions or exacerbation of psoriasis. Hair loss, although a causal relationship has not been established.
Musculoskeletal, connective tissue and bone disorders	
Very common	Musculoskeletal reactions (arthralgia, myalgia).

- If progressive skin rash occurs treatment with Terbinafine tablets should be discontinued.
- Any unusual or unexpected side effects should be reported immediately to the Irish Medicines Board.

4.9 Overdose

Based on the observed adverse effects in man, the main symptoms of an acute overdosage are likely to be gastrointestinal, e.g. nausea or vomiting. Gastric lavage and/or symptomatic supportive treatment may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco Therapeutic 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.

Efficacy in tinea capitis has not been established. Oral terbinafine is not effective in *Pityriasis versicolor*.

5.2 Pharmacokinetic 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 results in mean peak plasma concentrations of 1.3microgram/ml within 1.5 hours after administration.

At steady-state, in comparison to a single dose, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3. 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. When given orally, the medicinal product concentrates in skin and nails at levels associated with fungicidal activity.

Terbinafine binds strongly to plasma proteins (99%). 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.

The elimination rate may be reduced by 50% in patients with renal impairment (creatinine clearance <50mL/min) or hepatic impairment resulting in higher blood levels of terbinafine.

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 discontinuation of the medicinal product. 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
Croscarmellose sodium
Silica, colloidal anhydrous
Hypromellose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special requirements.

6.5 Nature and contents of container

Al/PVC/PVdC strip or HDPE Tablet Container with LDPE Cap
Pack sizes: 7, 14, 21, 28, 30, 42, 50, 60, 84, 100 or 500 tablets

Not all pack size 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

Medis ehf
Reykjavíkurvegur 78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1285/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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