1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

MYLAN TERBINAFINE 250 MG (tablets)

COMPOSITION:

Each **MYLAN TERBINAFINE 250 MG** tablet contains terbinafine hydrochloride equivalent to 250 mg terbinafine.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.2. Antimicrobial (Chemotherapeutic) agents. Fungicides.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

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.

Pharmacokinetics:

A single oral dose of 250 mg terbinafine results in mean peak plasma concentrations of 0,97 mg/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 is 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.

INDICATIONS:

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

1. **MYLAN TERBINAFINE 250 MG** tablets are 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.
2. **MYLAN TERBINAFINE 250 MG** tablets are indicated in the treatment of onychomycosis.

CONTRA-INDICATIONS:

Hypersensitivity to terbinafine hydrochloride or any of the excipients.

Impaired liver function.

Pregnancy and lactation, as safety has not been demonstrated.

INTERACTIONS:

The plasma clearance of terbinafine may be accelerated by drugs which induce metabolism (such as rifampicin) and may be inhibited by drugs which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such agents is necessary, the dosage of terbinafine tablets may need to be adjusted accordingly.

In vitro studies have shown, that terbinafine inhibits the CYP2D6-mediated metabolism. This *in vitro* finding may be of clinical relevance for patients receiving compounds predominantly metabolised by this enzyme, such as tricyclic antidepressants (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B.

Other studies undertaken *in vitro* and in healthy volunteers suggest that terbinafine shows negligible potential to inhibit or induce the clearance of drugs that are metabolised via other cytochrome P450 enzymes (e.g. ciclosporin, tolbutamine, terfenadine, triazolam, oral contraceptives). However, some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking terbinafine tablets concomitantly with oral contraceptives.

PREGNANCY AND LACTATION:

There is no clinical experience with terbinafine in pregnant women.

Terbinafine is excreted in breast milk and therefore mothers should not receive treatment with terbinafine whilst breast-feeding.

DOSAGE AND DIRECTIONS FOR USE:

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

250 mg once daily.

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:

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.

Impaired renal function:

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Haematological:

Very common: Neutropenia, thrombocytopaenia, agranulocytosis.

Central nervous system:

Very common: Headache.

Common: Paraesthesia, hypoaesthesia, dizziness, fatigue, malaise.

Psychiatric disturbances such as depression and anxiety.

Gastro-intestinal:

Very common: Dyspepsia, fullness, loss of appetite, nausea, abdominal pain and diarrhoea.

Common: Taste loss and taste disturbance.

Hepato-biliary disorders:

Common: Jaundice, cholestatis and hepatitis.

Musculoskeletal:

Rare: Arthralgia and myalgia.

Skin and subcutaneous tissue disorders:

More common: Rash, urticaria

Uncommon: Steven-Johnson Syndrome, toxic epidermal necrolysis, photosensitivity and angioneurotic oedema.

Special Precautions:

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within two months of starting treatment.

If a patient presents with signs or symptoms suggestive of liver dysfunction such as pruritis, unexplained persistent nausea, anorexia or tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine, or pale stools, hepatic origin should be verified and **MYLAN TERBINAFINE 250 MG** tablets should be discontinued. 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 **MYLAN TERBINAFINE 250 MG** tablets in patients with chronic or active liver disease has not been studied in prospective clinical trials, and therefore cannot be recommended.

Terbinafine should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

White to almost white, round, biconvex tablets with a score line on one side of the tablet.

PRESENTATION:

White Securitainers: 14, 28 and 100 tablets.

PVC/Aluminium Blisters: 14 and 28 tablets.

STORAGE CONDITIONS:

Store below 25 ºC. Protect from light.

The blister strips must not be removed from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A38/20.2.2/0691

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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