

## Summary of Product Characteristics

### 1. NAME OF THE MEDICINAL PRODUCT

Terbisil

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine as terbinafine hydrochloride.

For excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Tablet.

White, round, flat, 11.0mm tablets, scored on both sides with side scores, marked "T" above the score and "1" below the score on one side

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

1. Treatment of fungal infections sensitive to terbinafine such as Tinea corporis, Tinea cruris and Tinea pedis (caused by dermatophytes; see section 5.1) if considered appropriate due to the site, severity or extent of the infection.
2. The treatment of onychomycosis (terbinafine-sensitive fungal infection of the nails) caused by dermatophytes.

N.B. Orally administered terbinafine tablets are not effective against Pityriasis versicolor. The official local guidelines should be borne in mind, for example, national recommendations relating to the correct use and prescription of antimicrobial drugs.

#### 4.2 Posology and method of administration

Route of administration:

Oral use

The duration of treatment depends on the indication and the degree of severity of the infection.

Adults:

250 mg once daily.

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

For patients with hepatic impairment see section 4.3 and 4.4.

*Skin infections:*

The likely duration of treatment for Tinea pedis, Tinea corporis and Tinea cruris is 2 to 4 weeks.

For Tinea pedis (interdigital, plantar/moccasin-type): recommended treatment periods may be up to 6 weeks.

Complete disappearance of the symptoms of the infection may not occur until several weeks after mycological cure.

*Onychomycosis*

In most patients the duration of successful treatment is 6 to 12 weeks.

Fingernail onychomycosis:

In most cases 6 weeks' treatment is sufficient in fingernail onychomycosis.

Toenail onychomycosis:

In most cases 12 weeks' treatment is sufficient in toenail onychomycosis although a few patients may require treatment up to 6 months.

Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required. Complete resolution of 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 growth of a healthy nail.

*Children and adolescents (< 18 years)*

There is limited experience with oral terbinafine in children and adolescents and therefore its use cannot be recommended.

*Use in elderly*

There is no evidence to suggest that elderly patients require different dosages.

**4.3 Contra-indications**

Hypersensitivity to terbinafine or to any of the excipients.

Severe renal impairment.

Severe hepatic impairment.

**4.4 Special warnings and precautions for use**

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 terbinafine therapy should be discontinued (see section 4.8).

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine can be reduced by 50% (see section 5.2). 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.

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

Patients on terbinafine who develop a high fever or sore throat should be examined due to possible haematological reactions.

Terbinafine is a potent inhibitor of the isoenzyme CYP2D6, which should be taken into consideration if terbinafine is combined with medicinal products metabolised by this isoenzyme. (see section 4.5). Dose adjustments may be necessary.

#### **4.5 Interactions with other medicinal products and other forms of interaction**

The plasma clearance of terbinafine may be accelerated by active substances which induce metabolism (such as rifampicin) and may be inhibited by active substances which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such active substances is required, it may be necessary to adjust the dose of terbinafine accordingly.

In vitro studies have shown that terbinafine inhibits the CYP2D6 mediated metabolism. For this reason, it is important to monitor patients who are simultaneously treated with active substances that are mainly metabolised by this enzyme, such as tricyclic antidepressants, beta-blockers, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors Type B if the co-administered drugs have a narrow therapeutic index.

Other in vitro and clinical studies suggest that terbinafine shows negligible potential to inhibit or induce the clearance of active substances that are metabolised via other cytochrome P450 enzymes (e.g. ciclosporin, tolbutamine, terfenadine, triazolam, oral contraceptives). Some cases of menstrual disturbances such as breakthrough bleeding and irregular cycle in patients taking terbinafine concomitantly with oral contraceptives have been reported.

#### **4.6 Pregnancy and Lactation**

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

**Pregnancy:**

There is no clinical experience with terbinafine in pregnant women. Terbinafine should not be administered during pregnancy unless clearly necessary.

**Lactation:**

Terbinafine is excreted in breast milk and therefore, nursing mothers should not be given terbinafine whilst breast feeding. Breast-feeding should be discontinued before starting the treatment with terbinafine tablets.

#### **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 adverse reactions are usually mild to moderate and transient.

##### Blood and lymphatic system disorders:

Very rare (<1/10,000 inclusive isolated reports): Haematological disturbances such as neutropenia, agranulocytosis and thrombocytopenia.

##### Immune system disorders

Very rare (< 1/10,000): Manifestation or aggravation of cutaneous or systemic lupus erythematosus.

Very rare (< 1/10,000 including isolated reports): Anaphylactic reactions.

##### Psychiatric disorders

Very rare (<1/10,000 including isolated reports): Psychiatric disturbances such as depression and anxiety.

##### Nervous system disorders

Common (>1/100, <1/10): Headache.

##### Gastrointestinal disorders:

Common (>1/100 and <1/10): Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).

Uncommon (>1/1000 and <1/100): Taste disturbances, including loss of taste, that usually revert several weeks after withdrawal of the active substance. Isolated cases of persistent taste disturbances have been reported. In very few severe cases, a reduced intake of food causing significant loss of weight has been seen.

##### Hepatobiliary disorders:

Rare (>1/10,000 and <1/1000): Hepatobiliary dysfunction (primarily of cholestatic type).

Very rare (<1/10,000 inclusive isolated reports): Severe hepatic failure.

##### Skin and subcutaneous tissue disorders:

Common (>1/100 and <1/10): Non-serious skin reactions (rash, urticaria).

Rare (>1/10,000 and <1/1000): Severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity) and anaphylactoid reactions (incl. angioedema). If progressive rash occurs, the treatment with terbinafine should be discontinued.

Very rare (<1/10,000 including isolated reports): Exacerbation of psoriasis, loss of hair.

##### Musculoskeletal and connective tissue disorders:

Rare (>1/10,000 and <1/1000): Arthralgia and myalgia. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

## 4.9 Overdose

Few cases of overdose (up to 5 g) have been reported. The symptoms are headache, nausea, epigastric pain and dizziness.

The recommended treatment is elimination of the active substance, primarily by use of active charcoal and symptomatic treatment.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dermatologicals; antifungals for systemic use  
ATC code: D01B A02

Terbinafine is an allylamine having a broad-spectrum of antifungal activity. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity against yeasts is fungicidal or fungistatic depending on the species.

Terbinafine interferes selectively with fungal sterol biosynthesis at an early stage. This leads to a deficiency of ergosterole and to an intracellular accumulation of squalene in the fungal cell membrane. Both the deficiency in ergosterol and the accumulation of squalene are responsible for fungal cell death. Terbinafine also acts by inhibition of squalene epoxidase in the fungal cell membrane. When given orally, the active substance concentrates in skin, hair and nails, at levels associated with fungicidal activity. Measurable concentrations of the active substance are still evident 15 – 20 days after cessation of 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.

<u>Organism</u>	<u>MIC range (µg/ml)</u>
<i>Trichophyton rubrum</i>	0.001 – 0.15
<i>Trichophyton mentagrophytes</i>	0.0001 – 0.05
<i>Trichophyton verrucosum</i>	0.001 – 0.006
<i>Trichophyton violaceum</i>	0.001 – 0.1
<i>Microsporum canis</i>	0.0001 – 0.1
<i>Epidermophyton floccosum</i>	0.001 – 0.05

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

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

## **5.2 Pharmacokinetic properties**

Maximum plasma concentrations of 0.97 microgram/ml are obtained 2 hours after oral administration of a single dose of 250 mg terbinafine. The absorption half-life period is 0.8 hours and the distribution half-life period is 4.6 hours.

Terbinafine binds strongly to plasma proteins (99%).

It diffuses quickly through dermis and accumulates in the lipophilic stratum corneum. Terbinafine is also excreted in sebum, thus achieving high concentrations in hair follicles, hair and parts of the skin rich in sebaceous gland. There is also evidence that terbinafine is distributed into the nail plate within few weeks after initiation of treatment.

Terbinafine is rapidly metabolised by the CYP-isoenzymes, mainly by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. The biotransformation results in metabolites with no antifungal activities, which are excreted predominantly in the urine.

The elimination half-life is app. 17 hours. There is no evidence of accumulation in the plasma.

No age-related changes in pharmacokinetics have been observed, but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in increased plasma concentrations of terbinafine.

Single dose pharmacokinetic studies in patients with pre-existing mild to severe liver impairment have demonstrated that the clearance of terbinafine may be reduced by approximately 50%.

Although the bioavailability of terbinafine is moderately affected by food intake, dose adjustment is not necessary.

## **5.3 Preclinical safety data**

The approximate LD<sub>50</sub> value of terbinafine is over 4 g/kg in both mice and rats.

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 per day. At higher doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study with mice, no neoplastic or other abnormal findings attributable to treatment were found when doses of 130 (males) and 156 (females) mg/kg a day were administered.

In a two-year oral carcinogenicity study with rats, an increased incidence of liver tumours was observed in males at the highest dose level of 69 mg/kg per 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 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 with 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 following discontinuation of treatment. 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 undesirable effects on fertility or other reproduction parameters were observed in studies with rats or rabbits.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Microcrystalline cellulose  
Croscarmellose sodium  
Colloidal anhydrous silica  
Hypromellose  
Magnesium stearate

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

3 years.

### **6.4. Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5. Nature and Contents of Container**

Blisters (PVC/PVDC/aluminium) and HDPE tablet container with LDPE screw cap.

Pack sizes:

Blisters: 7, 10, 14, 28, 30, 42, 50, 56, 98, 112 tablets

Tablets container: 50 and 100 tablets.

Not all pack sizes may be marketed.

### **6.6. Instructions for use and handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Actavis Ltd.  
B16, Bulebel Industrial Estate,  
Zejtun, ZTN 08,  
Malta

**8. MARKETING AUTHORISATION NUMBER(S)**

MA245/00801

**9. DATE OF FIRST AUTHORISATION**

31st July 2006

**10. DATE OF REVISION OF THE TEXT**