# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Terbinafine 250mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg terbinafine, as terbinafine hydrochloride.

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

White, round, flat 11mm tablets, scored on both sides with side scores, marked "T" above and "1" below the score on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

1.Treatment of Terbinafine sensitive fungal infections such as Tinea corporis, Tinea cruris and Tinea pedis (caused by Dermatophytes see Section 5.1) is 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 is dependent on the indication and the degree of severity of the infection.
Adults:
250mg once daily.

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

*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.
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 6-12 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 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 growth of a healthy nail.

Children
A review of safety experience with oral terbinafine in children, which includes 314 patients involved in the UK LAMISIL® 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 has been noted. However, as data is still limited its use is not recommended.

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

## 4.3 Contraindications

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 pruritus, 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 4.8 Undesirable effects).

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

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 can not be recommended.

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

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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 drugs 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 treated simultaneously with drugs that are mainly metabolised by this enzyme, such as tricyclic antidepressants, β-blockers, selective serotonin re-uptake inhibitors and monoamine oxidase inhibitors type B if the co-medication has a narrow therapeutic index.

Other in vitro and clinical studies 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). There have been some cases reported of menstrual disturbances such as breakthrough bleeding and irregular cycle in patients taking Terbinafine concomitantly with oral contraceptives.

## 4.6 Pregnancy and lactation

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

Pregnancy:
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 terbinafine treatment whilst breast-feeding.

## 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

Gastrointestinal disorders
Common (>1/100, <1/10))
Dyspepsia, fullness, loss of appetite, nausea, mild abdominal pain, diarrhoea.

Skin-and subcutaneous tissue disorders
Common (>1/100, <1/10)
Allergic skin reactions (rash, urticaria).

Rare (>1/10,000, <1/1,000)
Serious skin reactions (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and angioneurotic oedema). If the skin rash is progressive then treatment with Terbinafine should be discontinued.

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

Nervous system disorders
Common (>1/100, <1/10)
Headache.

Rare (>1/10,000, <1/1,000)
Paraesthesia, hypoaesthesia, dizziness, malaise and fatigue.

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

Sensory disorders
Uncommon (>1/1,000, <1/100)
Taste loss and taste disturbances have been reported in approximately 0.6% of patients treated with Terbinafine. This usually resolves slowly on drug discontinuation.

Hepatobiliary disorders
Rare (>1/10,000, <1/1,000)
Serious hepatic dysfunction, including jaundice, cholestasis liver decompensation and hepatitis. If hepatic dysfunction develops, treatment with Terbinafine tablets should be discontinued (see also section 4.4. "Special warnings and precautions for use").

Blood and lymphatic system disorders
Very rare (<1/10,000), including isolated reports
Haematological disorders such as neutropenia, thrombocytopenia and agranulocytosis.

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

Immune system disorders
Very rare (< 0.01%)
Manifestation or aggravation of cutaneous or systemic lupus erythematosus

Respiratory
Very rare (<0.01%) including isolated reports
Anaphylactic reactions and angiooedema

### 4.9 Overdose

Few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. Recommended treatment for overdose consists of eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if required.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dermatologicals; antifungals for systemic use
ATC code: D01B A 02

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 selectively with fungal sterol biosynthesis at an early stage through inhibition of the enzyme squalene epoxidase. This leads to a deficiency in ergosterol 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.

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.

| Organism | MIC rang (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 |
| | |
| Epidermorphyton floccosum | 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.

## 5.2 Pharmacokinetic properties

A single oral dose of 250mg terbinafine results in mean peak plasma concentrations of 0.97 mcg/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 (99%).

Terbinafine 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 within a few weeks after commencing therapy.

Terbinafine is rapidly metabolised by the CYP-isoenzymes, mainly by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The elimination half-life is 17 hours. There is no evidence of accumulation in the plasma.

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.

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%.

The bioavailability of terbinafine is only slightly affected by food, and therefore a dose adjustment is not necessary.

## 5.3 Preclinical safety data

The approximate $LD_{50}$ 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 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 69 mg/kg, 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 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 active substance. 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 in rats or rabbits.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Magnesium stearate
Silica, colloidal anhydrous
Croscarmellose sodium
Hypromellose
Microcrystalline cellulose

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

36 months

## 6.4 Special precautions for storage

Blister Alu/PVC: Keep the blister in the outer carton
HDPE containers: store in the original package.

## 6.5 Nature and contents of container

Al/PVC-PVdC blister and HDPE tablet container with LDPE cap

Pack Sizes: 14, 28 tablets.
Not all container types or pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements

## 7. MARKETING AUTHORISATION HOLDER

Strandhaven Limited (T/A Somex Pharma)
600 High Road
Ilford
Essex
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER

PL 15764/0017

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th April 2005

## 10. DATE OF REVISION OF THE TEXT

July 2005