# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Terbinafine Pfizer 250 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine (as 281.25 mg terbinafine hydrochloride).

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, uncoated, biconvex bevelled edge tablets with breakline and ‘D’ debossed on one side and ‘74’ on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of fungal infections of the skin caused by terbinafine sensitive dermatophytes in cases of tinea corporis, tinea cruris and tinea pedis, when oral therapy is considered appropriate due to the site, severity or extent of the infection.

Treatment of onychomycosis caused by terbinafine sensitive dermatophytes.

Consideration should be given to official guidance concerning the appropriate use and prescription of antifungals.

### 4.2 Posology and method of administration

**Adults:**

250 mg once daily however, the duration of treatment will vary according to the indication and the severity of the infection.

**Skin Infections:**

Duration of the treatment

The likely durations of treatments are as follows:

Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks

Tinea corporis: 2 to 4 weeks

Tinea cruris: 2 to 4 weeks

**Onychomycosis:**

The duration of treatment is usually between 6 weeks and 3 months. Treatment of 6 weeks for onychomycosis of the finger nails is generally sufficient. Regarding onychomycosis of the toe nails, a 12 week treatment is usually sufficient, although a few patients with poor nail outgrow may require a longer treatment duration (6 months or longer). Complete resolution of the signs and symptoms of infection may not occur until several months after cessation of the treatment. This corresponds to the time needed for a healthy nail growth.

**Elderly:**

There is no evidence to suggest that elderly patients require a different dosage regimen or experience side effects different to those of younger patients. The possible impairment of liver or kidney function should be considered in this age group (see section 4.4).

**Renal insufficiency**

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

**Hepatic insufficiency:**

Terbinafine is not recommended for patients with chronic or active liver disease. In case of benefit-risk assessment the benefit overweighs the risks, a lower dosage should be initiated in case of hepatic insufficiency. In patients with pre-existing mild or serious liver disease clearance of terbinafine may be reduced (see section 5.2). See also section 4.4 with regard to patients with liver impairment.

**Method of administration:**

The tablet should be swallowed whole with water with or without food.

## 4.3 Contraindications

- Hypersensitivity to terbinafine or to any of the excipients.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.

## 4.4 Special warnings and precautions for use

The therapeutic use of terbinafine in patients with chronic or active liver disease has not been studied and is not recommended (see also section 4.2). Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that clearance of terbinafine may be reduced by about 50%. Where benefit outweighs the risks, a lower dosage should be initiated in case of hepatic insufficiency.

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within 2 months of starting treatment. Very rarely terbinafine can cause liver failure in patients with or without preexisting liver disease, which can lead to liver transplantation or death (hepatotoxicity). It is recommended that serum transaminase levels should be determined before the beginning of therapy, which can give indications of an acute or pre-existing liver disease. If a patient presents with signs or symptoms suggestive of liver dysfunction such as pruritus, persistent nausea, anorexia or tiredness, jaundice, vomiting, fatigue, abdominal pain or dark urine or pale stools, hepatic origin should be verified and treatment should be immediately stopped.

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

Terbinafine should be used with caution in patients with impaired renal function.

Patients with reduced renal function (creatinine clearance ≥30 < 50 ml/min or serum creatinine > 300 μmol/l) should receive half the normal dose.

Agranulocytosis and toxic epidermal necrolysis may very rarely occur in patients treated with oral terbinafine. Hence, patients should discontinue immediately the treatment and see a physician if the following symptoms occur : high fever, sore throat or other infections, pruritus, disseminated cutaneous disorders or cutaneous disorders with involvement of the mucosa (see section 4.8).

## 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). When co-administration of such agents is necessary, the dose of terbinafine 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 (TCAs), β-blockers, selective serotonin reuptake inhibitors (SSRIs), the antiarrhythmic agents (e.g. flecainide, propafenone) and monoamine oxidase inhibitors (MAO-Is) type B, These patients should be carefully monitored. *In vitro* terbinafine has been shown to be metabolised by at least 7 CYP-isoenzymes, mainly by the iso-enzymes CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.

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, tolbutamide, terfenadine, triazolam, oral contraceptives). However, some cases of menstrual disturbance (breakthrough bleeding and an irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives.

## 4.6 Fertility, pregnancy and lactation

***Pregnancy:***
Fetal toxicity and fertility studies in animals suggest no adverse effects.
There are no adequate data from the use of terbinafine in pregnant women, Therefore Terbinafine should not be given during pregnancy.

***Lactation:***
Terbinafine is excreted in breast milk and therefore nursing mothers should not receive Terbinafine whilst breast-feeding.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Adverse reactions are listed by frequency:

Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000),
not known (cannot be estimated from the available data)

The following undesirable effects have been observed:

***Investigations***:
*Common:* Increased hepatic enzymes level (see section 4.4).

***Blood and the lymphatic system disorders:***
*Very rare*: Agranulocytosis, neutropenia, thrombocytopenia.

***Nervous system disorders:***
*Common:* Headache.
*Rare:* Dizziness, hypoaesthesia, paresthesia.
*Very rare:* Vertigo

***Gastrointestinal disorders:***
*Common:* Fullness, mild abdominal pain, diarrhoea, dyspepsia, nausea.
*Uncommon*: Ageusia or dysgeusia (age over 65 years and low body mass index are risk factors), usually reversible within a few weeks or months after cessation of the treatment.
Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss.

***Skin and subcutaneous tissue disorders:***
*Very common:* Rash, urticaria.
*Very rare:* Serious skin reactions (e.g. Stevens-Johnson's syndrome, toxic epidermal necrolysis, photosensitivity and angioneurotic oedema) have been reported. If a progressive skin rash develops treatment should be discontinued.
Psoriasiform eruptions or exacerbation psoriasis.
Hair loss, although a causal relationship has not been established.

***Musculoskeletal, connective tissue and bone disorders:***
*Very Common*: Arthralgia and myalgia.
These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

***Metabolism and Nutritional disorders:***
*Common:* Anorexia (Loss of appetite).

***General disorders and administration site conditions:***
*Rare:* Fatigue, malaise.

***Immune system disorders:***
*Rare:* Incidence of allergic reactions (including anaphylaxis).

*Very rare:* Manifestation or aggravation of cutaneous or systemic lupus erythematosus.

***Hepato-biliary disorders:***
*Rare:* Hepatobiliary dysfunction especially cholestasis, and in rare cases liver failure, which in some instances has lead to hepatic transplantation or to death (see section 4.4).

***Reproductive system and breast disorders:***
Very rare: *Menstrual disturbance, breakthrough bleeding.*

***Psychiatric disorders:***
*Very rare:* Anxiety, depression.

## 4.9 Overdose

A few cases of overdose (up to 5 g) have been reported.
*Symptoms:*
Headache, nausea, epigastric pain and dizziness.

*Treatment*:
The recommended treatment of overdose consists of eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Dermatologicals: Antifungal 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.

Mechanism of action:
Terbinafine interferes specifically with fungal sterol biosynthesis at an early stage. 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. Terbinafine does not influence the metabolism of hormones or other drugs.

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

## 5.2 Pharmacokinetic properties

A single oral dose of 250 mg terbinafine results in mean peak plasma concentrations of 0.97µg/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%). 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 rapidly metabolised by 7 isoenzymes of the CYP-type, 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.

The bioavailability is about 80%, which is only slightly affected by food, and therefore a dose adjustment is not necessary.

## 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 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 malesat the highest dosage level of 69 mg/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 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 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

Cellulose, microcrystalline
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Hypromellose
Magnesium stearate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Store in the original package in order to protect from light.

## 6.5 Nature and contents of container

PVC/PVDC/Aluminum blister pack
Pack sizes: 7, 8, 14, 28, 30, 42, 56 and 98 tablets.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24

## 8 MARKETING AUTHORISATION NUMBER

PA 822/39/2

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

Date of first authorisation: 12th December 2008

## 10 DATE OF REVISION OF THE TEXT

February 2011