Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fungasil 250mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine (as hydrochloride).
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, or almost white round, biconvex tablets with a break line on one side and 250 engraved on the other.

The tablet can be divided into equal doses.

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) where oral therapy 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.
Consideration should be given to official guidance on the appropriate use of antifungal agents.

4.2 Posology and method of administration

Method 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.

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
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 different side effects than younger patients. When prescribing terbinafine tablets for patients in this age group, the possibility of pre-existing liver or kidney function impairment must be considered in this age group (see sections 4.4 and 4.8).

Liver impairment
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease (see sections 4.3 and 4.4).

Renal impairment
Use of terbinafine tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.3, 4.4 and 5.2).

4.3 Contraindications

· Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
· Severe renal impairment
· Chronic or acute hepatic impairment

4.4 Special warnings and precautions for use

Liver function
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing terbinafine tablets, liver function test should be performed. Hepatotoxicity may occur in patients with and without pre-existing hepatic disease therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended. Terbinafine should be immediately discontinued in case of elevation of liver function test. Very rare cases of serious hepatic failure (some with a fatal outcome, or requiring hepatic transplant) have been reported in patients treated with terbinafine tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine tablets was uncertain (see sections 4.3 and 4.8).

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

Patients prescribed terbinafine tablets should be warned to report immediately any signs and symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine, pruritus or pale faeces. Patients with these symptoms should discontinue taking oral terbinafine and the patient's hepatic function should be immediately evaluated (see section 4.8).

Dermatological effects
Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) have been very rarely reported in patients taking terbinafine tablets. If progressive skin rash occurs, terbinafine tablets treatment should be discontinued.

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

Haematological effects
Very rare cases of blood disorders (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with terbinafine tablets. Aetiology of any blood disorders that occur in patients treated with terbinafine tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with terbinafine tablets.

If severe changes in blood count, taste disorders or loss of the sense of taste or worsening skin reactions occur during terbinafine therapy, treatment must be stopped immediately.

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

A complete blood count should be considered in patients with known or presumed immune system weakness, which take terbinafine longer than 6 weeks.

Renal function
In patients with renal impairment (creatinine clearance less than 50 ml/min or serum creatinine of more than 300 micro mol/l) the use of terbinafine tablets has not been adequately studied, and therefore, is not recommended (see section 5.2).

Excipients
This medicinal Product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Effect of other medicinal products on terbinafine
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.

The following medicinal products may increase the effect or plasma concentration of terbinafine
Cimetidine decreased the clearance of terbinafine by 33%.

Fluconazole increased the C_{max} and AUC of terbinafine by 52% and 69% respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

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 drugs 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 irregular menstruation have been reported in patients taking terbinafine tablets 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. 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 (TCAs), β-blockers, selective serotonin re-uptake inhibitors (SSRIs), antiarrhythmics (including class 1A,

1B and 1C) and monoamine oxidase inhibitors (MAO-Is) type B and if the co-medication has a narrow therapeutic index. Dose adjustments may be necessary.

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

Pregnancy
Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience in pregnant women is very limited, terbinafine tablets should not be used during pregnancy unless clinical condition of the woman requires treatment with oral terbinafine and the potential benefits for the mother outweigh any potential risks for the foetus.

Breast-feeding
Terbinafine is excreted in breast milk; mothers receiving oral treatment with terbinafine should therefore not breast-feed.

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

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

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); 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).

Blood and lymphatic system disorders
Very rare: Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia.
Not known: Anaemia.

Immune system disorders
Rare: Anaphylactic reaction, serum sickness like reaction, angioedema.
Very rare: Anaphylactoid reaction, manifestation or aggravation of cutaneous or systemic lupus erythematosus.

Metabolism and nutrition disorders
Very common: Decreased appetite.
Common: Loss of appetite.

Psychiatric disorders
Very rare: Anxiety, depression (secondary to dysgeusia).

Nervous system disorders
Common: Headache
Uncommon: Dysgeusia, hypogeusia, ageusia (hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.).
Rare: Dizziness, hypoaesthesia, paraesthesia.
Not known: Anosmia.

Ear and labyrinth disorders
Not known: Hypoacusis, hearing impaired, tinnitus.

Vascular disorders

Not known: Vasculitis.

Gastrointestinal disorders
Very common: Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea.
Not known: Pancreatitis.

Hepatobiliary disorders
Rare: Cholestasis*, hepatic function abnormal*, hepatitis*, jaundice*, hepatic enzymes increased*, hepatic failure, followed by liver transplantation or death. In the majority of these cases patients suffered from a severe underlying disease.

Skin and subcutaneous tissue disorders
Very common: Rash, Urticaria.
Very rare: Erythema exsudativum multiforme (EEM), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP), photosensitivity reaction, psoriasiform eruptions or exacerbation of psoriasis*, alopecia.
Not known: Photodermatosis, photosensitivity allergic reaction and polymorphic light eruption.

Musculoskeletal and connective tissue disorders
Very common: Arthralgia, myalgia.
Not known: Rhabdomyolysis.

Reproductive system and breast disorders
Very rare: Menstruation irregular, breakthrough bleeding.

General disorders and administration site conditions
Common: Fatigue, malaise.
Not known: Influenza like illness, pyrexia.

Investigations
Not known: Blood creatinine phosphokinase increased, weight decreased (secondary to hypogeusia) *see section 4.4

Musculoskeletal disorders including arthralgia and myalgia have been reported. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.
Serious skin reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity.
Manifestation or aggravation of cutaneous or systemic lupus erythematosus.
Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 stagethrough 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 inergosterol and the accumulation ofsqualene 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
Epidermophyton 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

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 250 mg terbinafine resulted in mean peak plasma concentrations of 1.30µg/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.

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.

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 but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of terbinafine.

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50 ml/min) or with pre-existing liver disease have shown that clearance of terbinafine may be reduced by about 50%.

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

Cellulose microcrystalline
Hypromellose
Sodium starch glycolate
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Keep the blister in the outer carton.

6.5 Nature and contents of container

PVC/Aluminium blister: 7, 8**,** 14, 15, 28, 30, 42, 45, 98 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/141/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 August 2009
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