SUMMARY OF PRODUCT CHARACTERISTCS

1. NAME OF THE MEDICINAL PRODUCT

Fungasil 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Tablet

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

The tablet can be divided into equal halves.

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

Route of administration:

Oral use.

The duration of treatment is dependent 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/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
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. The possibility of pre-existing liver or kidney function impairment must be considered in this age group (see sections 4.4 and 4.8).

4.3 Contraindications

Hypersensitivity to Terbinafine or to any of the excipients
Severe renal impairment
Chronic or acute hepatic impairment

4.4 Special warnings and precautions for use

Pre-existing hepatic diseases should be determined before taking terbinafine.

In very rare cases terbinafine may cause liver failure in patients with or without a pre-existing hepatic disease, which could lead to liver transplantation or death (hepatic toxicity). It is therefore recommended to determine the serum transaminase values, which can give indications of an acute or pre-existing hepatic disease, before starting therapy with terbinafine (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. 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 immediately 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 (see sections 4.3 and 4.8).

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.

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.

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

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 Fertility, 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

a) Adverse effects are generally mild to moderate in severity and transient.
b)

Frequency → Primary System Organ Class (MedDRA 7.1) ↓	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000
Blood and lymphatic system disorders				Agranulocytosis Neutropenia Thrombocytopenia
Immune system disorders			Anaphylactic reaction Serum sickness like reaction (LLT)	Manifestation or aggravation of cutaneous or systemic lupus erythematosus (LLT)
Metabolism and nutrition disorders	Loss of appetite (LLT)			
Psychiatric disorders				Anxiety Depression
Nervous system	Headache	Ageusia	Dizziness	

disorders		Dysgeusia	Hypoaesthesia Paraesthesia	
Gastrointestinal disorders	Abdominal distension Abdominal pain Diarrhoea Dyspepsia Nausea			
Hepatobiliary disorders			Cholestasis* Hepatic function abnormal* Hepatitis* Jaundice*	Hepatic failure, followed by liver transplantation or death. In the majority of these cases patients suffered from a sever underlying disease
Skin and subcutaneous tissue disorders	Rash Urticaria		Angioneurotic oedema	Photosensitivity reaction Exacerbation of psoriasis (LLT)* Hair loss (LLT) Severe skin reactions, e.g. Stevens-Johnson syndrome Toxic epidermal necrolysis acute generalised exanthematous pustulosis (AGEP) and Erythema exsudativum multiforme (EEM)
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia			
Reproductive system and breast disorders				Menstruation irregular Breakthrough bleeding (LLT)
General disorders and administration site conditions	Fatigue Malaise			
Investigations			Hepatic enzyme increased*	

*see 4.4. Special warnings

c)

Musculo-skeletal 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 4.5. Interactions).

4.9 Overdose

Few cases of overdose (up to 5 g) 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 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.

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 range (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 250 mg 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

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. Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER

PA 126/141/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 12 August 2005

Date of last renewal: 7 April 2009

10. DATE OF REVISION OF THE TEXT

November 2010