Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nailderm 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains terbinafine hydrochloride, equivalent to 250 mg terbinafine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, round, biconvex tablet with TF scoreline 250 on one side and G on the other.
The score line is only to facilitate breaking for ease of swallowing and not to divide 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

Posology

Adults
250 mg once daily.
The duration of treatment is dependent on the indication and the degree of severity of the infection.

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 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.

Additional information on special populations

Paediatric population (0-17 years)
There is limited experience with oral terbinafine in children and adolescents and therefore its use cannot be recommended.

Liver impairment
Terbinafine tablets are contraindicated 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 sections 4.3, 4.4 and 5.2).

Elderly
There is no evidence to suggest that elderly patients (aged 65 years or above) 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 impairment of hepatic or kidney function should be considered (see section 4.4).

Method of administration

For oral use
The tablets are to be taken with water. They should preferably be taken at the same time each day and can be taken on an empty stomach or after a meal.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Liver function
Terbinafine tablets are contraindicated for patients with chronic or active hepatic disease.
Before prescribing terbinafine tablets, liver function test should be performed and any pre-existing liver disease should be assessed.

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).

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 liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with terbinafine tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions (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, decreased appetite, anorexia or fatigue, or jaundice, vomiting, fatigue, right upper abdominal pain or dark urine, or pale faeces, hepatic origin should be verified and terbinafine therapy should be discontinued (see section 4.8). Pretreatment serum transaminase tests (ALT, AST) are advised for all patients before taking terbinafine.

Haematological effects
Very rare cases of blood disorders (neutropenia, agranulocytosis, thrombocytopenia and 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.

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

Dermatological effects

Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms) 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 pre-existing psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

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).

Other

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

This medicine 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 medicinal products which induce metabolism (such as rifampicin) and may be inhibited by medicinal products which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such medicinal products 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 30%.
- 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

Terbinafine may increase the effect or plasma concentration of the following medicinal products:

Caffeine: Terbinafine decreased the clearance of caffeine administered intravenously by 21%.

Compounds predominantly metabolised by CYP2D6: *In vitro* and *in vivo* studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for patients receiving compounds predominantly metabolised by CYP2D6 e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin re-uptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, especially if they also have a narrow therapeutic window (see section 4.4).

Terbinafine decreased the clearance of desipramine by 82%.

In studies in healthy subjects characterised as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/ dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolisers (genotype) to poor metaboliser (phenotype) status.

Information on other drugs concomitantly used with terbinafine resulting in no or negligible interactions

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.

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further there was no clinically relevant interaction between terbinafine and the potential comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) 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 decrease the effect or plasma concentration of the following medicinal products:
- Terbinafine increased the clearance of ciclosporin by 15%.

Rare cases of changes in INR and/or prothrombin time have been reported in patients receiving terbinafine concomitantly with warfarin.

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 and therefore mothers should not receive treatment with terbinafine whilst breast-feeding.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of terbinafine tablets treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

Adverse effects are generally mild to moderate in severity and transient.
The following adverse reactions have been observed in the clinical trials or during post marketing experience.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Frequency → System Organ Class ↓	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia	Anaemia
Immune system disorders				Anaphylactic reactions, serum sickness-like reaction	Anaphylactoid reaction, angioedema, cutaneous and systemic lupus erythematosus	

Frequency → System Organ Class ↓	Very common	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders	Decreased appetite					
Psychiatric disorders					Anxiety, depressive symptoms	
Nervous system disorders		Headache	Dysgeusia* including ageusia*	Dizziness, hypoaesthesia, paraesthesia		Anosmia including permanent anosmia, hyposmia.
Eye disorders						Visual impairment, vision blurred, visual acuity reduced
Ear and labyrinth disorders					Vertigo	Hypoacusis, impaired hearing, tinnitus
Vascular disorders						Vasculitis
Gastrointestinal disorders	Feeling of fullness abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea)					Pancreatitis
Hepatobiliary disorders				Cases of serious hepatic dysfunction, including hepatic failure, hepatic enzymes increased, jaundice, cholestasis and hepatitis***		
Skin and subcutaneous tissue disorders	Rash, urticaria				Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxic skin eruption, dermatitis exfoliative, dermatitis bullous, acute generalised exanthematous pustulosis (AGEP), Psoriasiform eruptions or exacerbation of psoriasis (see 4.4).	Drug rash with eosinophilia and systemic symptoms

Frequency → System Organ Class ↓	Very common	Common	Uncommon	Rare	Very rare	Not known
					Alopecia. If progressive skin rash occurs, terbinafine treatment should be discontinued. Photosensitivity reactions.	
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia					Rhabdomyolysis
Reproductive system and breast disorders					Menstruation irregular, breakthrough bleeding (see 4.5)	
General disorders and administration site conditions		Fatigue		Malaise		Influenza like illness, pyrexia
Investigations			Weight decreased**	Hepatic enzyme increased (see section 4.4)		Blood creatinine phosphokinase increased

*Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.
** Weight decreased secondary to dysgeusia
***If hepatic dysfunction develops, treatment with terbinafine should be discontinued (see also section 4.4). Very rare cases of serious liver failure have been reported (some with a fatal outcome, or requiring liver transplant). In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine was uncertain.

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, Website: www.hpra.ie

4.9 Overdose

Symptoms
A few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, upper abdominal pain and dizziness.

Treatment
The recommended treatment of overdosage consists in eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dermatologicals; antifungals for systemic use, ATC code: D01BA02

Mechanism of action

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 specifically with fungal sterol biosynthesis at an early step. 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.

Pharmacodynamic effects
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
Edidermorphyton fluccosum	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

Absorption
Following oral administration, terbinafine is well absorbed (> 70 %) and the absolute bioavailability of terbinafine from 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 1.30 mcg/ml within 1.5 hours after administration. Plasma concentrations decline in a triphasic manner, with a terminal half-life of 16.5 days. At 28 days, when around 70% steady state levels have been achieved, peak concentrations of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3 when compared to single dose administration. 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.

Distribution
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 the first few weeks of commencing therapy.

Biotransformation

Terbinafine is metabolised rapidly and extensively by at least seven CYP-isoenzymes, with major contributions by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine.

Other special populations

Elderly
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.

Effects in renal and hepatic impairment
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 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 69mg/kg a 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 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

Silica, colloidal anhydrous
Croscarmellose sodium
Magnesium stearate
Cellulose, microcrystalline
Povidone K29-32
Talc

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

PVC/Aluminium blister pack, containing 7, 8, 14, 28, 30, 42, 56, 98, 100 or 250 tablets
HDPE bottles with PP caps, containing 7, 8, 14, 28, 30, 42, 56, 98, 100, or 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd., T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/068/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 28th July 2009

10 DATE OF REVISION OF THE TEXT

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