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

Fungal infections of the skin caused by Trichophyton (e.g. *T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum*) *Microsporum canis* and *Epidermophyton floccosum.*

Oral Terbinafine tablets are indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis where oral therapy is considered appropriate due to the site, severity or extent of the infection.

The treatment of onychomycosis (terbinafine-sensitive fungal infection of the nails) caused by dermatophyte fungi.

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 varies according to the indication and the degree of severity of the infection.

Skin infections
The likely durations of treatment are as follows:

Tinea pedis (interdigital, plantar/moccasin-type): 2 to 6 weeks
Tinea corporis: 4 weeks
Tinea cruris : 2 to 4 weeks

Onychomycosis
The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infections, toenail infection other than of the big toe, or patiens of younger age.

In the treatment of toenail infection, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. 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.

Special populations

Paediatric population
There is no data available in children under 2 years of age (usually <12kg).

Children weighing >40kg 250mg(one 250mg tablet) once daily

This formulation is not recommended in children weighing 20-40kg (dose of 125mg) as the tablets cannot be broken into two equal halves, and other formulations should be used.

Hepatic impairment
Terbinafine tablets are contraindicated for patients with chronic or active hepatic disease (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Renal impairment
The use of terbinafine tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Elderly
There is no evidence to suggest that elderly patients (aged 65 years or above) require different dosages or experience different side effects to those of 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

Known hypersensitivity to terbinafine or to any of the excipients listed in section 6.1.
Severe renal impairment.

4.4 Special warnings and precautions for use

Liver function
Terbinafine tablets are contraindicated for patients with chronic or active liver disease.
Before prescribing terbinafine tablets, liver function test should be performed and any pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease.

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 liver failure cases the patients had serious underlying systemic conditions (see section 4.3 Contraindications and section 4.8 Undesirable effects). Patients prescribed terbinafine tablets should be warned to report immediately any symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, jaundice, dark urine or pale faeces. Patients with these symptoms should discontinue taking oral terbinafine and the patient's liver function should be immediately evaluated.

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

Haematological effects
Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia and pancytopenia) have been reported in patients treated with terbinafine tablets. Aetiology of any blood dyscrasias 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.

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, treatment with terbinafine tablets should be discontinued.

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as precipitation and exacerbation of psoriasis and cutaneous and systemic lupus erythemaosus have been reported in a post-marketing setting.

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 Pharmacokinetic properties).

Interactions
In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolised by this enzyme, e.g. certain members of the following drug classes, tricyclic antidepressants (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics class IC and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed, if the co- administered drug has a narrow therapeutic window (see 4.5 Interaction with Other Medicaments and Other Forms of Interaction).

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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. Where co-administration of such agents is neccessary, the dosage of terbinafine may need to be adjusted 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%.

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 irregularities 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. This finding may be of clinical relevance for 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 Special warnings and precautions for use).

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 to poor metaboliser status.

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

Women of child-bearing potential
Some cases of menstrual irregularities 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.

There is no data to support special recommendations for women of child-bearing potential.

Pregnancy:
Foetal toxicity studies in animals suggest no adverse effects. Since documented 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
There is no relevant information from human experience. Fertility studies in rats indicated no adverse findings in fertility or reproductive performance.

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

In general Terbinafine tablets are well tolerated. Side effects are usually mild to moderate and transient. The following adverse reactions have been observed in the clinical trials or during post marketing experience.

Adverse drug reactions from clinical trials or post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on 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 (frequency cannot be estimated from the available data).

Frequency → System Organ Class ↓	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and			Anaemia		Neutropenia,	

lymphatic system disorders					agranulocytosis, thrombocytopenia, pancytopenia	
Immune system disorders				Anaphylactic reactions, serum sickness-like reaction	Anaphylactoid reactions (including angioedema, cutaneous and systemic lupus erythematosus)	
Psychiatric disorders		Depression	Anxiety			
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			Tinnitus			Hypoacusis, impaired hearing
Vascular disorders						Vasculitis
Gastrointestinal disorders	Gastrointestinal symptoms (abdominal distension, decreased appetite, mild abdominal pain, diarrhoea, dyspepsia, nausea)					Pancreatitis
Hepatobiliary disorders				Hepatic failure, hepatic enzymes increased (see section 4.4 warnings and precautions for use), jaundice, cholestasis and hepatitis		
Skin and subcutaneous tissue disorders	Rash, urticaria		Photosensitivity reaction		Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxic skin eruption, dermatitis exfoliative, dermatitis bullous, Psoriasiform eruptions or	Drug rash with eosinophilia and systemic symptoms

					exacerbation of psoriasis Alopecia.	
Musculoskeletal and connective tissue disorders	Musculoskeletal reactions (arthralgia, myalgia)					Rhabdomyolysis
General disorders and administration site conditions		Fatigue	Pyrexia			Influenza like illness
Investigations			Weight decreased**			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

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

Based on the observed adverse effects in man, the main symptoms of an acute overdosage are likely to be gastrointestinal, e.g. nausea or vomiting. Gastric lavage and/or symptomatic supportive treatment may be required.

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 squlalene epoxidase in the fungal cell membrane.

The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

Efficacy on tinea capitis has not yet been established.

Oral terbinafine is not effective in *Pityriasis versicolor*.

Onychomycosis
The efficacy of Terbinafine Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials (SFD301, SF5 and SF1508).

Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or > 5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).

In a second toenail study of dermatophytic onychomycosis, in which non-dermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.

The mean time to treatment success for onychomycosis was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing Terbinafine therapy, the clinical relapse rate was approximately 15%.

Fungal infections of the skin (Tinea corporis, Tinea cruris, Tinea pedis) and yeast infections of the skin caused by the genus Candida (e.g. Candida albicans) where oral therapy is generally considered appropriate owing to the site, severity or extent of the infection

Three controlled, double blind, randomised, multicenter studies 5OR (4 week study), 6-7OR (4 week study) and 11-21OR (6 week study), evaluated efficacy and safety of Terbinafine tablets in the treatment of Tinea corporis and cruris.

Two double blind, placebo controlled studies (5OR, 6-7OR) evaluated the efficacy of Terbinafine 125mg b.i.d.in patients diagnosed with Tinea corporis/cruris. The studies included a total of 46 patients randomised to Terbinafine and 49 on placebo. There was no significant difference in terms of demographic and anamnestic data within groups. Efficacy, demonstrated by negative mycology tests and a reduction in clinical symptomatology, was evaluated at 4 weeks and at the follow-up examination. In both studies, minimal efficacy was demonstrated in patients treated with placebo compared to the efficacy of orally administered Terbinafine at the end of therapy and at follow up.

The third study (11-21OR), a 6 weeks, double blind, randomised, multicenter study compared efficacy and safety of Terbinafine 125mg b.i.d. to griseofulvin 250mg b.i.d. One hundred twenty six (126) patients in each group were included in the efficacy analysis. This study showed high rate of mycological cure, reduction in signs and symptoms in the Terbinafine treated study arm and significantly better (93-94%) overall efficacy at the end of therapy and at follow up of Terbinafine 125mg b.i.d. compared to 86-87% overall efficacy of comparator.

In summary, Terbinafine 125mg b.i.d. administered for the period of 4-6 weeks demonstrated statistically superior efficacy compared to placebo and marketed drug griseofulvin in the treatment of Tinea corporis/cruris in the above major efficacy studies.

In a double blind, placebo controlled 4 weeks study SF 00438, Terbinafine 125 b.i.d was compared to placebo in patients with cutaneous candidiasis. Twenty two patients were randomised to each treatment arm, of which 19 were evaluated respectively. Of those, 29% of patients in the treatment arm and 17% of patients on placebo demonstrated mycological cure at the end of treatment and 67% of Terbinafine treated patients had negative mycological results at the end of follow up. Given the above response rates, 2 weeks therapy of Terbinafine should be the minimum duration of treatment period and approximately half of the patients would require 3-4 weeks of treatment to achieve cure.

Two double blind, controlled studies compared Terbinafine 125mg b.i.d. to placebo (39-40OR) and to griseofulvin 250mg b.i.d. (20OR) in the treatment of Tinea pedis. Both studies recruited patients with chronic, recurrent disease. In the study 39-40OR, 65% of patients on Terbinafine reported mycological cure at follow up whereas none of the placebo treated patients responded. In the study 20OR, Terbinafine was shown to be highly effective with 88% of cure at follow up after 6 weeks therapy compared to 45% of patients on griseofulvin. These patients when observed after 10 months reported 94% cure rate, compared to 30% efficacy of griseofulvin in the same patient population.

Table 2 Major efficacy studies – Tinea corporis/cruris, Tinea pedis, Candida infections

Study		Type		Drug		No. of evaluable patients			Dropouts		Mycological results% negative End Rx F/up		Clinical results End Rx F/up	
5OR	4wk DB-placebo		Lamisil 125 b.i.d		13 15		4 2	64 0		89 0		54 0		62 0

			Placebo											
6-7OR	4wk DB-placebo		Lamisil125 b.i.d Placebo		33 34		8 6	97 29		97 36		85 12		91 12
11-21OR	6wk 125 b.i.d. DB-Griseofulvin		Lamisil 125 b.i.d Griseofulvin 250 b.i.d		126 126		13 16	95 88		100 94		93 87		94 86
SF 00438	2wk DB-placebo		Lamisil 125 b.i.d Placebo		19 19		3 3	29 17		67 47		11 11		47 11
39-40OR	6wk 125 b.i.d. DB-placebo		Lamisil 125 b.i.d Placebo		23 18		3 6	68 13		77 0		59 0		65 0
20OR	6wk 125 b.i.d. DB-Griseofulvin		Lamisil 125 b.i.d Griseofulvin 250 b.i.d		16 12		2 6	94 27		100 55		75 27		88 45

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 a mean peak plasma concentration of 1.3 microgram/mL within 1.5 hours of administration. At steady-state (70% steady state is achieved in approximately 28 days), 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. When given orally, the drug accumulates in skin and nails at levels associated with fungicidal activity.

Distribution

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.

Biotransformation

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. Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days.

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 the clearance of terbinafine may be reduced by about 50%.

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 100mg/kg a day. At high oral doses, the liver and possibly also the kidney 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 a day. 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 or other studies in mice, dogs or monkeys.

During high-dose studies in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic levels 50 mg/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.
An 8-week oral study in juvenile rats provided a no-toxic-effect level (NTEL) of close to 100 mg/kg/day, with the only finding being slightly increased liver weights, while in maturing dogs at ≥100 mg/kg/day (AUC values about 13x (m) and 6x (f) those in children), signs of central nervous system (CNS) disturbance including single episodes of convulsions in individual animals were observed. Similar findings have been observed at high systemic exposure upon intravenous administration of terbinafine to adult rats or monkeys.

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

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin

Ireland

8 MARKETING AUTHORISATION NUMBER

PA23266/037/001

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

November 2024