Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lanafine 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

Fungal infections of the skin caused by *Trichophyton* (eg. *T. rubrum, T.mentagrophytes, T. Verrucosum, T. Violaceum*).
Microsporum canis and *Epidermophyton floccosum*.

1. Oral terbinafine is 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.

2. Oral terbinafine is indicated in the treatment of onychomycosis.

4.2 Posology and method of administration

Adults:
250mg once daily.
The duration of treatment varies according to the indication and the severity of the infection.

Skin infections
Likely duration 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

Onychmycosis:
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 infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficent 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.

Additional information on special population

Liver impairment

Lanafine tablets are not recommended for patients with chronic or active liver disease (see section 4.4 Special warnings and precautions for use).

Renal impairment

The use of Lanafine 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).

Children

A review of safety experience with oral terbinafine in children has shown that the adverse event profile in children is similar to that seen in adults. No evidence of any new, unusual or more severe reactions to those seen in the adult population have been noted. However, as data is still limited its use is not recommended.

Elderly

There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group (see Precautions).

Method of administration
Via the oral route.

4.3 Contraindications

Known hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings and precautions for use

Liver Function

Lanafine tablets are not recommended for patients with chronic or active liver disease. Before prescribing Lanafine tablets, 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 Lanafine tablets. In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Lanafine tablets was uncertain (see section 4.8 Undesirable effects).

Patients prescribed Lanafine tablets should be instructed to report immediately any 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. Patients with these symptoms should discontinue taking oral terbinafine and the patient's liver function should be immediately evaluated.

Dermatological effects

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

Haematological effects

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

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50%.

Terbinafine should be used with caution in patients with 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 Lanafine tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).

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 and may be inhibited by drugs which inhibit cytochrome P450. Where co-administration of such agents is necessary, 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 30%.

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

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. tolbutamine, terfenadine, triazolam, 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 menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives.

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 (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B.

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%.

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

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

There is no clinical experience with terbinafine in pregnant women, therefore unless the potential benefits outweigh any potential risks, Terbinafine should not be administered during pregnancy.

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

No studies on the effects of Lanafine 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

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

Adverse reactions are ranked under headings of frequency, 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), including isolated reports.

Blood and lymphatic system disorders	
Very rare	Neutropenia, agranulocytosis, thrombocytopenia.
Not known	Pancytopenia
Immune system disorders	
Very rare	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.
Psychiatric disorders	
Very rare	Psychiatric disturbances (such as depression and anxiety)
Nervous system disorders	
Common	Headache
Uncommon	Taste disturbances, including taste loss, which usually recover slowly after discontinuation of the drug. Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss.
Rare	Paraesthesia, hypoaesthesia, dizziness
Ear and labyrinth disorders	

Very rare	Vertigo
Gastrointestinal disorders	
Very common	Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).
Hepatobiliary disorders	
Rare	Cases of serious hepatic dysfunction, including jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with terbinafine should be discontinued (see also Section 4.4 Special Warnings and Precautions for Use). 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.
Skin and subcutaneous tissue disorders	
Very common	Non-serious forms of skin reactions (rash, urticaria).
Very rare	Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity). If progressive skin rash occurs, terbinafine treatment should be discontinued.
Not known	Psoriasiform eruptions or exacerbation of psoriasis. Serious skin reactions (e.g. acute generalized exanthematous pustulosis).
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal reactions (arthralgia, myalgia).
General disorders	
Rare	Malaise
Not known	Fatigue

Other adverse drug reactions from post-marketing spontaneous reports

The following adverse drug reactions have been identified based on post marketing spontaneous reports and are organized by system organ classes.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and lymphatic system disorders: anaemia.

Immune system disorders: anaphylactic reaction, serum sickness-like reaction.

Nervous system disorders: anosmia including permanent anosmia, hyposmia.

Vascular disorders: vasculitis.

Gastrointestinal disorders: pancreatitis.

Musculoskeletal and connective tissue disorders: rhabdomyolysis.

General disorders and administration site conditions: influenza-like illness, pyrexia.

Investigations: blood creatine phosphokinase increased.

4.9 Overdose

A few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. The recommended treatment of overdosage consists in 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: Oral antifungal agent (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 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.

When given orally, the drug concentrates in skin at levels associated with fungicidal activity.

5.2 Pharmacokinetic properties

A single oral dose of 250 mg terbinafine results in mean plasma concentrations of 0.97 μg/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. 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 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.

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 of terbinafine is unaffected by food.

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 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. 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-doses 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 found in studies in rats and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline PH101 and PH102
Hypromellose
Sodium starch glycolate (type A)
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The folded carton of Terbinafine 250 mg tablet contains 8, 14, 28, 42 and 98 tablets. Not all pack sizes may be marketed. The blister is made of aluminium/PVC.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited,
1 The Cam Centre, Wilbury Way,
Hitchin, Hertfordshire, SG4 OTW,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1063/018/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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