NOVARTIS

LAMISIL®

(Terbinafine)

250 mg, Tablet

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1. NAME OF THE MEDICINE

Lamisil® 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 250 mg tablet contains 250 mg terbinafine as terbinafine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LAMISIL® 250 mg tablet (scored): a whitish to yellow-tinged white, circular, biconvex, bevelled edged tablet, scored on one side and coded LAMISIL 250 (circular) on the other side, with smooth or slightly rough surface. Diameter approximately 11 mm.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Fungal infections of the skin caused by dermatophytes such as *Trychophyton (e.g. T. rubrum, T. mentagrorophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum*.

Oral LAMISIL® is indicated in the treatment of ringworm (*Tinea corporis, Tinea cruris* and *Tinea pedis)* and yeast infections of the skin caused by Candida (e.g., *Candida albicans*) where topical treatment is considered inappropriate owing to the site, severity, or extent of the infection.

Onychomycosis (fungal infection of the nail) caused by dermatophyte fungi.

Children:

Tinea capitis.

Note: In contrast to topical LAMISIL®, oral LAMISIL® is not effective in pityriasis versicolor and also not in gastro-intestinal and vaginal candidiasis.

4.2 Posology and method of administration

Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained from the nail bed to confirm the diagnosis of onychomycosis.

The duration of treatment varies according to the indication and the severity of the infection.

Posology

Adults

250 mg once a day.

Skin infections

Recommended duration of treatment:

Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks.

Tinea corporis, *T. cruris*: 2 to 4 weeks.

Cutaneous candidiasis: 2 to 4 weeks.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

Hair and scalp infections

Recommended duration of treatment:

Tinea capitis: 4 weeks.

Tinea capitis occurs primarily in children.

Onychomycosis

For most patients, the duration of successful treatment is 6-12 weeks.

Fingernail onychomycosis: Six weeks of therapy is sufficient for fingernail infections in most cases.

Toenail onychomycosis: Twelve weeks of therapy is sufficient for toenail infections in most cases.

Some patients with poor nail outgrowth may require longer treatment. The optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for outgrowth of healthy nail.

Special populations

Liver impairment

LAMISIL® tablets are not recommended for patients with chronic or active liver disease (see Section 4.4).

Renal impairment

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 µmol/L) the use of LAMISIL® tablets has not been adequately studied, and therefore, is not recommended in this population (see section 5.2).

Elderly

There is no evidence that elderly patients require different dosages or experience different side-effects than younger patients. When prescribing LAMISIL® tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see above).

Paediatric population

No data are available in children under two years of age (usually < 12 kg).

Children weighing under 20 kg: 62,5 mg once daily (the use of Lamisil 250 mg tablets is not recommended).

Children weighing 20-40 kg: 125 mg (half 250 mg tablet) once daily.

Children weighing more than 40 kg: 250 mg once daily.

Method of administration

The scored tablets are taken orally 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 terbinafine and any of the excipients of LAMISIL® tablets.

Impaired liver function.

Breastfeeding (see Section 4.6).

4.4 Special warnings and precautions for use

Cutaneous and mucosal Candida infection, pityriasis versicolor

Orally administered terbinafine is not active or is insufficiently active against skin infections caused by *Candida spp.* or *Pityrosporum ovale* (pityriasis versicolor) or against mucosal infections caused by *Candida spp.* (including vaginal candidosis).

Liver function

LAMISIL® tablets are not recommended for patients with chronic or active liver disease. Before prescribing LAMISIL® tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver transplant and has been reported in patients treated with LAMISIL® tablets. Therefore, periodic

monitoring (after 4-6 weeks of treatment) of the liver function is recommended. In the majority of liver failure cases, the patients had serious underlying systemic conditions and a causal association with the intake of LAMISIL® tablets was uncertain (see Section 4.9). Patients prescribed LAMISIL® tablets should be warned to report immediately any symptoms of unexplained persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale stools. Patients with these symptoms should discontinue taking oral LAMISIL® and the patient's liver function should be immediately evaluated.

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 LAMISIL® tablets. If progressive skin rash occurs, LAMISIL® tablets treatment should be discontinued.

Caution is recommended in the use of terbinafine in patients with existing psoriasis or lupus erythematosus, given that very rare cases of cutaneous and systemic lupus erythematosus and psoriasiform eruptions or exacerbation of psoriasis have been reported.

Haematological effects

Cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with LAMISIL® tablets. The

etiology of every blood disorder that occurs in patients who are treated with LAMISIL® tablets must be evaluated and a possible adjustment of the medication schedule must be considered, including discontinuation of the treatment with LAMISIL® tablets. It is recommended to monitor blood cells frequently.

Cases of thrombotic thrombocytopenic purpura (TTP), some fatal, have been reported with terbinafine. Discontinue terbinafine if clinical symptoms and laboratory findings consistent with TTP occur. The findings of unexplained thrombocytopenia and anemia should prompt further evaluation and consideration of the diagnosis of TTP.

Renal function

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 µmol/L) the use of LAMISIL® tablets has not been adequately studied, and therefore, is not recommended in this population (see section 5.2).

4.5 Interaction with other medicines and other forms of interaction

Terbinafine is an inhibitor of CYP2D6. An interaction is possible with medications that are primarily metabolised via CYP2D6 such as tricyclic antidepressants, beta blockers, selective serotonin reuptake inhibitors (SSRI), antiarrhythmic drugs (including class 1A, 1B and 1C) and type B monoamino-oxidase inhibitors (MAOI). Patients must be monitored, especially if the therapeutic window for these medications

is small (see Section 4.5).

Checking of the blood count for immunodeficient patients who have been under treatment for longer than 6 weeks.

Effect of other medicines on LAMISIL®:

The plasma clearance of LAMISIL® may be accelerated by medicines, which induce metabolism and may be inhibited by medicines, which inhibit cytochrome P450.

Where co-administration of such medicines is necessary, the dosage of LAMISIL® tablets may need to be adjusted accordingly.

The following medicines may increase the effect or plasma concentration of LAMISIL®

Cimetidine decreased the clearance of LAMISIL® by 33 %.

Fluconazole increased the Cmax and AUC of LAMISIL® by 52 % and 69 % respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other medicines which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with LAMISIL®.

The following medicines may decrease the effect or plasma concentration of LAMISIL®

Rifampicin increased the clearance of LAMISIL® by 100 %.

Effect of LAMISIL® on other medicines:

According to the results from studies undertaken *in vitro* and in healthy volunteers, LAMISIL® shows negligible potential for inhibiting or enhancing the clearance of medicines that are metabolised via the cytochrome P-450 system (e.g., terfenadine, triazolam, tolbutamide or oral contraceptives).

LAMISIL® does not interfere with the clearance of antipyrine or digoxin.
LAMISIL® has no effect on the pharmacokinetics of fluconazole. There is no clinically relevant interaction between LAMISIL® and cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline. Cases of menstrual irregularities have been reported in patients taking LAMISIL® tablets concomitantly with oral contraceptives.

LAMISIL® may increase the effect or plasma concentration of the following medicines:

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

Compounds predominantly metabolised by CYP2D6:

In vitro and *in vivo* studies have shown however, that LAMISIL® inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for compounds predominantly metabolised by CYP2D6, such as tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antidysrhythmics (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)

LAMISIL® decreased the clearance of desipramine by 82 %. LAMISIL® increased the dextromethorphan metabolic ratio in urine by 16- to 97- fold on average in studies in healthy subjects characterised as extensive metabolisers of dextromethorphan (antitussive medicines).

Thus, LAMISIL® may convert extensive CYP2D6 metabolisers to poor metaboliser status.

LAMISIL® may decrease the effect or plasma concentration of the following medicines:

LAMISIL® increased the clearance of ciclosporin by 15 %.

Drug-food/drink interactions

The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20 %), but not sufficiently to require dose adjustments.

4.6 Fertility, pregnancy and lactation

Pregnancy

In an observational, registry-based cohort study, there was no increase in the risk of major malformations or spontaneous abortion in pregnancies exposed to oral terbinafine in comparison to those not exposed to oral terbinafine (see clinical data).

In animal reproduction studies, terbinafine did not cause reproductive toxicity in rats and rabbits at oral doses up to 12 and 23 times the maximum recommended human dose (MRHD) based on body surface (BSA), respectively (see non-clinical data).

The use of terbinafine may be considered during pregnancy, if necessary.

Data

Clinical Data

A nationwide, observational, registry-based cohort study was conducted in a cohort of 1,650,649 pregnancies. Pregnancies were matched on propensity scores comparing pregnancies exposed to oral terbinafine versus those not exposed to oral terbinafine in a 1:10 ratio to evaluate the risk of major malformations (522 versus 5220) and spontaneous abortions (891 versus 8910).

The prevalence odds ratio for the risk of major malformations was 1,01 (95 % CI, 0,63-1,62) for pregnancies exposed versus not exposed to oral terbinafine. The hazard ratio for the risk of spontaneous abortion was 1,06 (95 % CI, 0,86-1,32) for the same comparison. No increased risk of major malformations or spontaneous abortion was identified among pregnancies exposed to oral terbinafine.

Non-clinical data

In embryo-foetal development studies in rats and rabbits, terbinafine was administered orally (30, 100, or 300 mg/kg/day) during the period of organogenesis. There were no embryotoxic or teratogenic effects up to the maximum tested dose of 300 mg/kg/day in rats and rabbits (corresponding to 12 and 23 times the MRHD based

on BSA, respectively). Subcutaneous administration of terbinafine (10, 30 or 100 mg/kg/day) to rats during the period of organogenesis showed no teratogenic or embryotoxic effect up at doses up to 100 mg/kg/day (corresponding to 4 times the MRHD based on BSA).

In a rat peri- and postnatal development study, oral administration of terbinafine (30, 100 or 300 mg/kg/day) had no adverse effects on pregnancy and lactation at doses up to 300 mg/kg/day (corresponding to 12 times the MRHD based on BSA). No treatment related effects in F1 and F2 generations were noted.

Breastfeeding

LAMISIL® is excreted in breastmilk. Mothers receiving oral treatment with LAMISIL® tablets should not breastfeed their infants.

There is no data on the effects of terbinafine on the breastfed child or on milk production. The maximum ratio of terbinafine in milk to plasma is 7:1, and the maximum amount of terbinafine ingested by the infant is expected to be 16 % of the dose administered to the nursing mother. The highest concentration of terbinafine in breast milk was observed within 6 hours after administration, and thereafter the concentration of terbinafine decreased by approximately 70 % in the 6–12-hour time window after administration.

Fertility

There is no relevant information from human experience. Studies regarding fertility in animals did not reveal any toxic effect.

4.7 Effects on ability to drive and use machines

No studies on the effects of LAMISIL® 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 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.

Table 1: Adverse reactions from clinical trials and post-marketing experience

Blood and lymphatic system disorders	
Uncommon:	Anaemia.
Very rare:	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia
Unknown:	Thrombotic thrombocytopenic purpura
Immune system disorders	

Very rare:	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus
Unknown:	Anaphylactic reactions, serum sickness-like reaction
Psychiatric disorders	
Common:	Depression
Uncommon:	Anxiety
Nervous system disorders	
Very common:	Headache
Common:	Taste disturbances (Dysgeusia* including ageusia*), dizziness
Uncommon:	Paraesthesia and hypoesthesia
Unknown:	Anosmia including permanent anosmia, hyposmia
Eye disorders	
Common:	Visual impairment.
Unknown:	Vision blurred, visual acuity reduced
Ear and labyrinth disorders	
Uncommon:	Tinnitus.
Unknown:	Hypoacusis
Gastrointestinal disorders	
Very common:	Gastrointestinal symptoms (abdominal distension, decreased appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).

Unknown:	Pancreatitis
Hepatobiliary disorders	
Rare:	Hepatobiliary dysfunction liver failure, hepatitis, jaundice, cholestasis, increased liver enzymes
Skin and subcutaneous tissue disorders	
Very common:	Non-serious forms of skin reactions (Rash, urticaria).
Uncommon:	Photosensitivity reaction.
Very rare:	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP), toxic skin eruption, dermatitis exfoliative, dermatitis bullous. Psoriasiform eruptions or exacerbation of psoriasis Alopecia
Unknown:	Drug rash with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders	
Very common:	Musculoskeletal reactions (arthralgia, myalgia)
Unknown:	Rhabdomyolysis
General disorders and administration site conditions	
Uncommon:	Pyrexia
Common:	Fatigue
Unknown:	Illnesses resembling influenza
Tests	

Uncommon:	Weight loss**
Unknown:	Increased blood creatinine phosphokinase

* Hypogeusia, including ageusia, which generally recovers within several weeks after treatment with the medication has been discontinued. Isolated cases of long-term hypogeusia have been reported.

**Weight loss as a result of dysgeusia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See Undesirable effects.

Cases of overdosage (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain, and dizziness.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.2. Antimicrobial (Chemotherapeutic) agents. Fungicides.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, terbinafine is well absorbed (> 70 %). 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.

Although the intake of food has a slight influence on the biological availability of terbinafine, an adjustment of the dosage is not necessary. 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.

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/metabolism

Terbinafine is metabolised rapidly and extensively by at least seven CYP iso-enzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8, CYP2C19 and CYP2D6.

Elimination

Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. Plasma concentrations decline in a triphasic manor, with a

terminal half-life of 16,5 days.

Bioavailability

The absolute bioavailability of terbinafine from LAMISIL® tablets as a result of first-pass metabolism is approximately 50 %.

Special population

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.

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

Repeat dose toxicity

In long-term studies (up to 1 year) in rats and dogs, no pronounced toxic effects were noticed in either animal with an oral dosage of 100 mg/kg/day. At a high oral dosage, the liver and possibly also the kidneys are identified as potential target organs.

Mutagenicity and carcinogenicity

A standard series of *in vitro* and *in vivo* genotoxicity tests did not yield any signs of mutagenicity or clastogenic potential.

In a two-year oral carcinogenicity study, no abnormal findings were observed that could be connected to the treatment with dosages up to 130 (males) and 156 (females) mg/kg/day.

In a two-year oral carcinogenicity study in rats an increased incidence of liver tumours was observed in males with the highest dosage content of 69 mg/kg/day. The changes that were attributed to peroxisome proliferation were not species-specific because they were not observed during the carcinogenicity study in mice or in other studies with mice, dogs or monkeys.

During a study with a high dosage in monkeys, refraction problems were observed in the retina with higher dosages (non-toxic effect level of 50 mg/kg). These issues were attributed to the presence of terbinafine metabolite in the ocular tissue and disappeared after discontinuation of treatment. They were not attributed to histological changes.

Juvenile animal studies

An 8-week oral study in juvenile rats determined a non-toxic effect level (NTEL) of almost 100 mg/kg/day, with only a finding of slightly increased liver weight, while in adult dogs with ≥100 mg/kg/day (AUC levels of about 13x (m) and 6x (w) in children), signs of central nervous system (CNS) dysfunction, including several episodes of convulsions in individual animals, were observed. The same findings were observed with high systemic exposure following intravenous administration of terbinafine to

adult rats and monkeys.

Reproductive toxicity

In a fertility and reproductive study, rats were treated orally with terbinafine (10, 50, or 250 mg/kg/day) starting 9 weeks (males) or 2 weeks (females) prior to mating and continued through pregnancy and lactation. There were no effects on fertility or general reproductive performance. However, at 250 mg/kg/day (corresponding to 10 times the MRHD based on BSA), there was evidence of parental toxicity (reduced body weight gain, lower pregnancy rate and litter size), increased pre- and perinatal offspring mortality, and retarded postnatal offspring development. For information on embryofoetal and pre- and postnatal toxicity, see section 4.6.

6. PHARMACUETICAL PARTICULARS

6.1 List of excipients

Magnesium stearate; silica colloidal anhydrous; hydroxypropylmethyl cellulose; microcrystalline cellulose; sodium carboxymethyl starch.

6.2 Shelf-life

3 years

6.3 Special precautions for storage

Store in a cool, dry place below 30 °C. Protect from light.

6.4 Nature and contents of the container

Blister pack of 14.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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