SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

LAMISIL® 125 mg tablet

LAMISIL® 250 mg tablet

COMPOSITION:

Active ingredient:

Each 125 mg tablet contains 125 mg terbinafine as terbinafine hydrochloride.

Each 250 mg tablet contains 250 mg terbinafine as terbinafine hydrochloride

List of excipients

LAMISIL® 125 mg:

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

LAMISIL® 250 mg:

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

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.2. Antimicrobial (Chemotherapeutic) agents. Fungicides.

PHARMACOLOGICAL 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. Its activity against 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 cell

death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P-450 system.

Pharmacokinetics:

A single oral dose of 250 mg terbinafine results in peak plasma concentrations of 1.3 microgram/mL within 1.5 hours of administration.

At steady-state, 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 affected by food but dose adjustments are not required.

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

Biotransformation results in metabolites with no antifungal activity, which is excreted predominantly in the urine.

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 %.

INDICATIONS:

Adults:

Fungal infections of the skin caused by dermatophytes such 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.

CONTRA-INDICATIONS:

Hypersensitivity to terbinafine and any of the excipients of LAMISIL® tablets.

Impaired liver function.

Pregnancy and lactation.

INTERACTIONS:

Effect of other medicinal products 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 agents is necessary, the dosage of LAMISIL® tablets may need to be adjusted accordingly.

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

Cimetidine decreased the clearance of LAMISIL® by 33%.

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

Rifampicin increased the clearance of LAMISIL® by 100%.

Effect of LAMISIL® on other medicinal products:

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 digoxin.

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 medicinal products:

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 serotonine reuptake 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 special precautions for use.)

LAMISIL® decreased the clearance of desipramine by 82%.

LAMISIL® may decrease the effect or plasma concentration of the following medicinal products

LAMISIL® increased the clearance of ciclosporin by 15%.

PREGNANCY AND LACTATION:

Pregnancy

LAMISIL® is contra indicated in pregnancy as safety has not been demonstrated.

Lactation

LAMISIL® is excreted in breast milk; mothers receiving oral treatment with LAMISIL® tablets should therefore not breast-feed.

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.

DOSAGE AND DIRECTIONS FOR USE:

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

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

Children (*with Tinea capitis*):

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

Children weighing under 20 kg

62,5 mg (half 125 mg tablet) once daily

Children weighing 20-40 kg

125 mg (one 125 mg tablet) once daily

Children weighing more than 40 kg

250mg (two 125 mg tablets) once daily

Adults:

125 mg twice a day or 250 mg once a day

Skin infections

Recommended duration of treatment:

Tinea pedis (interdigital, plantar/moccasin type):

2 to 6 weeks.

Tinea corporis, 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.

Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of big toenail, and in patients of younger age.

In the treatment of toenail infections, 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.

In fungal nail infections, 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 tissue.

Limited experience is available for periods longer than 6 months.

Additional information on special population

Liver impairment

LAMISIL® tablets are not recommended for patients with chronic or active liver disease (see "Special Precautions").

Renal impairment

In patients with renal impairment (creatinine clearance less than 50mL /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 Pharmacokinetic properties)

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).

SIDE-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.

General disorders

Very rare:

Fatigue

Blood and the lymphatic system disorders

Very rare:

Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia

Immune system disorders

Very rare:

Anaphylactoid reactions (including angioedema). Cutaneous and systemic lupus erythematosus.

Nervous system and psychiatric disorders

Very rare:

Dizziness, paraesthesia and hypoaesthesia.

Uncommon:

Taste disturbances, including taste loss, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged taste disturbances have been reported. A decrease of food intake leading to significant weight loss was observed in very few severe cases.

Common:

Headache

Hepato-biliary disorders

Rare:

Hepatobiliary dysfunction (primarily cholestatic in nature), including very rare cases of serious liver failure (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 LAMISIL® tablets was uncertain.

Gastrointestinal disorders

Very common**:**

Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).

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, acute generalized exanthematous pustulosis)

Psoriasiform eruptions or exacerbation of psoriasis.

Hair loss, although a causal relationship has not been established.

Musculoskeletal, connective tissue and bone disorders

Very common:

Musculoskeletal reactions (arthralgia, myalgia).

Special Precautions:

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 disease. Cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with LAMISIL® tablets. 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 “Side-effects”). 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) have been very rarely reported in patients taking LAMISIL® tablets. If progressive skin rash occurs, LAMISIL® tablets treatment should be discontinued.

Haematological effects

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with LAMISIL® tablets. In the event of any of the above, LAMISIL® tablets should be discontinued.

Renal function

In patients with renal impairment (creatinine clearance less than 50mL /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 Pharmacokinetic properties)

Interactions with other medicinal products

In vitro and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with medicines predominantly metabolised by CYP2D6, e.g. certain members of the following drug classes: tricyclic antidepressants (TCAs), beta-blockers, selective serotonine reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed up especially, if the co-administered drug has a narrow therapeutic window. (See Interaction with other medicinal products and other forms of interaction).

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

Other

LAMISIL® 125 mg tablets contain lactose (21 mg/tablet). Patients with problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take LAMISIL® 125 mg tablets.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See side-effects.

A few 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.

IDENTIFICATION:

LAMISIL® 125 mg tablet (scored) for use in children: A whitish to white-tinged yellow, circular, biconvex, bevelled edged tablet, scored and coded LP on one side, with smooth or slightly rough surface. Diameter approximately 9mm.

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 11mm.

PRESENTATION:

LAMISIL® 125 mg tablets: Blister pack of 14.

LAMISIL® 250 mg tablets: Blister pack of 14

STORAGE INSTRUCTIONS:

Store in a cool, dry place. Store at or below 30 °C. Protect from light. Keep out of reach of children.

REGISTRATION NUMBERS:

LAMISIL® 125 mg tablets: Z/20.2.2/184

LAMISIL® 250 mg tablets: Z/20.2.2/185

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West

Waterfall City

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2090

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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