APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

SOUTH AFRICA: S4

NAMIBIA: NS2

PROPRIETARY NAME (and dosage form):

BINACIL 125 mg (tablet)

BINACIL 250 mg (tablet)

COMPOSITION:

BINACIL 125 mg: Each uncoated tablet contains terbinafine hydrochloride equivalent to terbinafine 125 mg.

BINACIL 250 mg: Each uncoated tablet contains terbinafine hydrochloride equivalent to terbinafine 250 mg.

The other ingredients of the formulation include cellulose microcrystalline, sodium starch glycolate, colloidal anhydrous silica, hypromellose, and magnesium stearate.

PHARMACOLOGICAL CLASSIFICATION:

A20.2.2. Antimicrobial (Chemotherapeutic) agents. Fungicides.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain fungi. The activity 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 medicine concentrates in skin at levels associated with fungicidal activity.

Pharmacokinetics:

A single oral dose of 250 mg terbinafine results in mean peak 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.

INDICATIONS:

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

BINACIL 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.
- onychomycosis.

CONTRA-INDICATIONS:

- Hypersensitivity to terbinafine hydrochloride or any of the excipients.
- Impaired liver function.
- Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

- **BINACIL** should not be used in patients with existing liver disease and liver function tests should be performed in all patients before starting therapy. If clinical or biochemical indications of hepatotoxicity appear, **BINACIL** should be discontinued.

- **BINACIL** should also be discontinued if a progressive skin rash appears.
- **BINACIL** should be used with caution and in reduced doses in patients with renal impairment (see **"DOSAGE AND DIRECTIONS FOR USE"**).
- **BINACIL** may provoke or exacerbate psoriasis. **BINACIL** should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

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, anorexia, tiredness, jaundice, vomiting, fatigue, abdominal pain, dark urine, or pale stools, hepatic origin should be verified and **BINACIL** should be discontinued. Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of **BINACIL** may be reduced by about 50 %. The therapeutic use of **BINACIL** in patients with chronic or active liver disease has not been studied in prospective clinical trials, and therefore cannot be recommended.

Effects on ability to drive and use machines

There are no data regarding the ability to drive vehicles and use machinery. However, caution is advised when using **BINACIL** before the effect on the patient is established, especially since dizziness and fatigue may be experienced.

INTERACTIONS:

The plasma clearance of **BINACIL** may be accelerated by medicines which induce metabolism (such as rifampicin) and may be inhibited by medicines which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such medicines is necessary, the dosage of **BINACIL** may need to be adjusted accordingly. It has been reported that **BINACIL** inhibits the CYP2D6-mediated metabolism. This *in vitro* finding may be of clinical relevance for patients receiving medicines predominantly metabolised by this enzyme, such as tricyclic antidepressants (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B. Other studies undertaken *in vitro* and in healthy volunteers suggest that **BINACIL** shows negligible potential to inhibit or induce the clearance of medicines that are metabolised via

other cytochrome P450 enzymes (e.g. ciclosporin, triazolam, oral contraceptives). However, some cases of menstrual disturbance (breakthrough bleeding and irregular cycles) have been reported in patients taking **BINACIL** concomitantly with oral contraceptives.

PREGNANCY AND LACTATION:

BINACIL is contra-indicated in pregnancy. Terbinafine is excreted in breast milk and therefore mothers who receive treatment with **BINACIL** should not breast-feed their infants (see **"CONTRA-INDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

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

250 mg once daily.

Skin infections:

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 infection, toenail infection other than of the big toe, or 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. Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

Children:

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.

Impaired renal function:

Patients with impaired renal function (creatinine clearance less than 50 ml/minute or serum creatinine of more

than 300 mmol/l) should receive half the normal dose.

SIDE EFFECTS:

Blood and the lymphatic system disorders:

Less frequent: Neutropenia, thrombocytopenia and agranulocytosis.

Immune system disorders:

Less frequent: Angioedema.

Psychiatric disorders:

Less frequent: Psychiatric disturbances such as depression and anxiety.

Nervous system disorders:

Frequent: Headache.

Less frequent: Paraesthesia, hypoaesthesia, dizziness and vertigo.

Gastrointestinal disorders:

Frequent: Loss of appetite, nausea, mild abdominal pain, diarrhoea.

Less frequent: Taste loss and taste disturbance have been reported in approximately 0,6% of patients treated with **BINACIL.** This usually resolves slowly on medicine discontinuation.

The following side effects have been reported but the frequencies are unknown: Dyspepsia and fullness.

Hepato-biliary disorders:

Less frequent: Jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with **BINACIL** should be discontinued (see **"Special Precautions"**).

Skin and subcutaneous tissue disorders:

Less frequent: Stevens-Johnson syndrome, toxic epidermal necrolysis, rash, urticaria, photosensitivity and psoriasis. If progressive skin rash occurs, treatment with **BINACIL** should be discontinued.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Arthralgia and myalgia. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

General disorders and administrative site conditions:

Less frequent: Malaise and fatigue.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

A few cases of overdose (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 drug, primarily by the

administration of activated charcoal, and giving symptomatic supportive therapy if needed.

IDENTIFICATION:

BINACIL 125 mg: White to off-white, round uncoated, biconvex bevelled edge tablets having 'D' debossed on one side and '56' on the other side.

BINACIL 250 mg: White to off-white round uncoated, biconvex bevelled edge tablets with break line and 'D' debossed on one side and '74' on the other side.

PRESENTATION:

BINACIL 125 mg:

Tablets are packed in clear 250 microns PVC coated with 60 gsm PVdC and 25 microns printed Aluminium foil. One blister contains 14 tablets.

Pack size: 14's - Each carton contains 1 blister of 14 tablets each.

BINACIL 250 mg:

Tablets are packed in clear 250 microns PVC coated with 60 gsm PVdC and 25 microns printed Aluminium foil. One blister contains 14 tablets.

Pack size: 14's - Each carton contains 1 blister of 14 tablets each.

STORAGE CONDITIONS:

Store at or below 30°C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

SOUTH AFRICA:

BINACIL 125 mg: 42/20.2.2/0471

BINACIL 250 mg: 42/20.2.2/0472

NAMIBIA:

BINACIL 125 mg: 10/20.2.2/0261

BINACIL 250 mg: 10/20.2.2/0262

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

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1,

53 Phillip Engelbrecht Avenue,

Meyersdal, Ext. 12, 1448,

Johannesburg,

South Africa

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