NAME OF APPLICANT/PHCR	: CIPLA MEDPRO (PTY) LTD.
PRODUCT PROPRIETARY NAME	: LAMISPOR 250
DOSAGE FORM	: TABLET
DOSAGE STRENGTH	: 250 mg

PART 1C LABELLING

a) Package Insert

The under-mentioned information with regard to this medicine shall appear on the scientific package insert. The information shall be presented in the format stipulated: Provided that the Council may authorize any deviation from such information or such format (refer to Regulation 9).

1. Scheduling status
2. Proprietary name and dosage form
3. Composition
4. Pharmacological classification
5. Pharmacological action
   (Pharmacokinetics, pharmacodynamics and summary of clinical studies, where applicable)
6. Indications
7. Contra-indications
8. Warnings
9. Interactions
10. Pregnancy and lactation
11. Dosage and directions for use
12. Side effects and special precautions
13. Known symptoms of overdosage and particulars of its treatment
14. Identification
15. Presentation
16. Storage instructions
17. Registration number
18. Name and business address of the holder of the certificate of registration
19. Date of publication of the package insert

1. Proposed Package Insert **1C-002**

PROPOSED PACKAGE INSERT FOR

LAMISPOR 250

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

LAMISPOR 250 (Tablets).

COMPOSITION:

Active Ingredient: Each tablet contains 250 mg terbinafine as terbinafine hydrochloride.

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 mg/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.*

(LAMISPOR) 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, as safety has not been demonstrated.

INTERACTIONS:

The plasma clearance of **(LAMISPOR)** may be accelerated by medicines which induce metabolism (such as rifampicin) and may be inhibited by drugs which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such agents is necessary, the dosage of **(LAMISPOR)** may need to be adjusted accordingly.

It has been reported that **(LAMISPOR)** inhibits the CYP2D6-mediated metabolism. This *in vitro* finding may be of clinical relevance for patients receiving compounds 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 **(LAMISPOR)** shows negligible potential to inhibit or induce the clearance

of drugs that are metabolised via other cytochrome P450 enzymes (e.g. ciclosporin, tolbutamine, terfenadine, triazolam, oral contraceptives). However, some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking **(LAMISPOR)** concomitantly with oral contraceptives.

PREGNANCY AND LACTATION:

There is no clinical experience with **(LAMISPOR)** in pregnant women. Terbinafine is excreted in breast milk and therefore mothers should not receive treatment with **(LAMISPOR)** whilst breast-feeding.

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

Tineo 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 AND SPECIAL PRECAUTIONS:

Side-effects:

Gastrointestinal Disorders:

***Frequent*:** Dyspepsia, fullness, loss of appetite, nausea, mild abdominal pain, diarrhoea.

Taste loss and taste disturbance have been reported in approximately 0,6 % of patients treated with **(LAMISPOR)**. This usually resolves slowly on medicine discontinuation.

Nervous System Disorders:

Less frequent: Psychiatric disturbances such as depression and anxiety, headache. Paraesthesia, hypoaesthesia, dizziness, vertigo, malaise and fatigue

Skin and subcutaneous disorders:

Less frequent: Stevens-Johnson syndrome, toxic epidermal necrolysis, rash, urticaria,photosensitivity and angioneurotic oedema, psoriasis.

If progressive skin rash occurs, treatment with **(LAMISPOR)** should be discontinued.

Hepato-biliary disorders:

Frequent: Jaundice, cholestasis and hepatitis.

If hepatic dysfunction develops, treatment with **(LAMISPOR)** should be discontinued (see also **"PRECAUTIONS FOR USE"**).

Haematological disorders:

Less frequent: Neutropenia, thrombocytopenia and agranulocytosis.

Other side-effects reported include:

Musculoskeletal disorders including arthralgia and myalgia. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

Special Precautions:

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

(LAMISPOR) should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

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 in eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

IDENTIFICATION:

LAMISPOR 250 mg Tablet: White, circular, biconvex uncoated tablets, with deep score on one side and plain on the other side.

PRESENTATION:

LAMISPOR 250 mg Tablets: Supplied in white opaque PVC and aluminium foil blister strips of 14 tablets.

STORAGE CONDITIONS:

Store below 25°C. Protect from light.

STORE THIS MEDICINE OUT OF REACH OF CHILDREN.

Keep the blisters in the outer carton until required for use.

REGISTRATION NUMBER:

To be allocated.

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

CIPLA MEDPRO (PTY) LTD
Rosen Heights
Pasita Street
Rosen Park, Bellville
7530, R.S.A.

DATE OF PUBLICATION OF THIS PACKAGE INSERT