1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MICROCIDAL - 125 (tablet)

MICROCIDAL - 500 (tablet)

COMPOSITION

Each tablet of MICROCIDAL - 125 contains 125 mg of griseofulvin.

Excipients:

Colloidal silicone dioxide, lactose monohydrate, magnesium stearate, pregelatinised starch, purified talc, starch maize

Contains sugar: Lactose monohydrate 14,6 mg

Each tablet of MICROCIDAL **-** 500 contains 500 mg of griseofulvin.

Excipients:

Colloidal silicone dioxide, lactose monohydrate, magnesium stearate, pregelatinised starch, purified talc, starch maize

Contains sugar: Lactose monohydrate 140,0 mg

CATEGORY AND CLASS

A 20.1.7 Antifungal antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Griseofulvin is fungistatic *in vitro* for various species of the dermatophytes *Microsporum, Epidermophyton,* and *Trichophyton*. The drug has no effect on bacteria or on other fungi.

A prominent morphologic manifestation of the action of griseofulvin is the production of multinucleate cells as the drug inhibits fungal mitosis. Griseofulvin causes disruption of the mitotic spindle by interacting with polymerized microtubles. Although the effects of the drug are thus similar to those of colchicine and the vinca alkaloids, its binding sites on the microtubular protein are distinct. There is evidence that griseofulvin binds to a microtubule-associated protein in addition to its binding to tubulin. Although failure of ringworm lesions to improve is not rare, isolates from these patients usually are still susceptible to griseofulvin *in vitro*.

Pharmacokinetic properties

The oral administration of a 0,5 g dose of griseofulvin produces peak plasma concentrations of approximately 1 µg/ml in about 4 hours. Blood levels are quite variable.

Griseofulvin has a half-life in plasma of about 1 day, and approximately 50 % of the oral dose can be detected in the urine within 5 days, mostly in the form of metabolites. The primary metabolite is 6-methylgriseofulvin. Barbiturates decrease the absorption of griseofulvin from the gastrointestinal tract.

The drug is deposited in keratin precursor cells. The antibiotic present in such cells when

they differentiate is tightly bound to, and persists in, keratin and makes this substance resistant to fungal invasion. For this reason, the new growth of hair or nails is the first to become free of disease. As the fungus-containing keratin is shed, it is replaced by normal tissue. Griseofulvin is detectable in the stratum corneum of the skin within 4 to 8 hours or oral administration. Sweat and transepidermal fluid loss play an important role in the transfer of the drug in the stratum corneum. Only a very small fraction of a dose of the drug is present in body fluids and tissues.

INDICATIONS

Mycotic diseases of the skin, hair and nails due to *Microsporum, Trichophyton* or *Epidermophyton,* respond to MICROCIDAL therapy.

It must be stressed that, since other fungal diseases are not affected by the medicine, careful mycological study with identification of the responsible organism is the only basis on which therapy can be selected accurately.

Also infections of the scalp (tinea capitis) caused by *M.canis, M.audouini, T.schoenleinii,* and *T.verrucosum;* "ringworm" of the glabrous skin: tinea cruris and tinea corporis caused by *M.canis, T.rubrum, T.verrucosum and E.floccosum;* and tinea of the hands (*T.rubrum, T. mentagrophytes*) and beard (*Trichophyton* species) are readily treatable with MICROCIDAL.

MICROCIDAL also is highly effective in "athlete's foot" or epidermophytosis involving the skin and nails, the vesicular form of which is most commonly due to *T.mentagrophytes* and the hyperkeratotic type of *T.rubrum, Trichophyton rubrum* and *T.mentagrophytes* infections may require higher-than-conventional doses.

CONTRAINDICATIONS

- Porphyria. It may precipitate an acute attack.

- Liver failure.
- Pregnancy. MICROCIDAL crosses the placenta and it has been shown to be embryo toxic and teratogenic in rats.
- Hypersensitivity to MICROCIDAL.

WARNINGS AND SPECIAL PRECAUTIONS

Men receiving MICROCIDAL should not father children within six months of treatment. The warning is based on data from *in vitro* studies using mammalian cells which demonstrated aneuploidy.

Use with extreme caution in patients with systemic lupus erythematosus, as MICROCIDAL may precipitate or aggravate it.

Effects on ability to drive and use machines

MICROCIDAL may impair the ability to drive or operate machinery (see INTERACTIONS).

Excipients

Lactose warning:

MICROCIDAL contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take MICROCIDAL.

INTERACTIONS

- Phenobarbitone has been reported to decrease the gastrointestinal absorption of MICROCIDAL.
- MICROCIDAL may increase the rate of metabolism and diminish the side effects of

some drugs such as coumarin anticoagulants and oral contraceptives.

- MICROCIDAL has also been reported to reduce the plasma concentrations of salicylate in patients taking aspirin.
- Since MICROCIDAL is derived from a species of *Penicillium,* it is theoretically possible that patients intolerant to penicillins or penicillamine may be intolerant of MICROCIDAL also. However, cross-sensitivity between MICROCIDAL and penicillins or penicillamine has not been clinically substantiated. In addition, penicillin-sensitive patients have received MICROCIDAL without difficulty.
- MICROCIDAL has been reported to enhance the effects of alcohol.

HUMAN REPRODUCTION

The safety of MICROCIDAL in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

MICROCIDAL crosses the placenta and it has been shown to be embryo toxic and teratogenic in rats.

Men receiving MICROCIDAL should not father children within six months of treatment. The warning is based on data from *in vitro* studies using mammalian cells which demonstrated aneuploidy.

Use of an alternate or additional means of contraception if taking oestrogen-containing oral contraceptives concurrently with MICROCIDAL and for one month after stopping MICROCIDAL therapy is advisable.

DOSAGE AND DIRECTIONS FOR USE

Adults: 500 mg to 1 g per 24 hours. Doses of 1,5 g to 2,0 g per 24 hours may be used

for short periods in severe or extensive infections.

Children: 10 mg/kg per 24 hours.

Take with or after meals, especially fatty meals, in order to minimize possible gastrointestinal irritation and to increase absorption.

Best results are obtained when the daily dose is divided and given at 6-hour intervals.

Treatment must be continued until infected tissue is replaced by normal hair, skin or nails, which required 2 to 6 months for skin and hair infections, 6 to 9 months for fingernails, and at least a year for toenails.

SIDE EFFECTS

Side effects are usually mild and transient. They consist of headache, skin rashes, dryness of the mouth, an altered sensation of taste, and gastrointestinal disturbances.

Angioedema, erythema multiform, toxic epidermal necrolysis, proteinuria, leucopenia and other blood dyscrasias, candidiasis, paraesthesia, photosensitisation, and severe headache have been reported occasionally. Depression, confusion, dizziness, insomnia, and fatigue have also been reported.

Reports of hepatotoxicity have been attributed to MICROCIDAL. Oral thrush, granulocytopenia or leucopenia and peripheral neuritis can also occur less frequently.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

The symptoms of overdosage are those stated under side effects above and in these cases the dosage should be reduced or the medicine discontinued.

Treatment

Treatment is supportive and symptomatic.

IDENTIFICATION

MICROCIDAL - 125: A round, white, flat, bevelled edged tablet, bisected on the one side and engraved with a mortar and pestle on the other side.

MICROCIDAL - 500: A round, white, biconvex tablet, engraved with a mortar and pestle.

PRESENTATION

MICROCIDAL - 125:

100 tablets are packed in a white polypropylene container and sealed with a low density polyethylene cap together with a rayon or foam insert.

28 tablets are packed into patient ready packs in low density polyethylene Ziplock lay-flat bags or printed Metallised lay-flat bags. The packed bank bags are grouped, packed and sealed into polyethylene bags together with a leaflet.

MICROCIDAL - 500:

30 or 100 tablets are packed in a white polypropylene container and sealed with a low density polyethylene cap together with a rayon or foam insert.

28 tablets are packed into patient ready packs in low density polyethylene Ziplock lay-flat

bags or printed Metallised lay-flat bags. The packed bank bags are grouped, packed and sealed into polyethylene bags together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C in airtight, well-closed containers.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

MICROCIDAL - 125: K/20.1.7/218

MICROCIDAL - 500: K/20.1.7/219

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

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration:

MICROCIDAL - 125: 16 May 1978

MICROCIDAL - 500: 16 May 1978

Date of the most recent amendment to the professional information as approved by the

Authority: 16 May 1978

Botswana:	S2
MICROCIDAL - 125:	B9322505
MICROCIDAL - 500:	B9322515

Namibia:	NS2
MICROCIDAL - 125:	90/20.1.7/001054
MICROCIDAL - 500:	90/20.1.7/001055

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