GRISOVIN™
Griseofulvin

QUALITATIVE AND QUANTITATIVE COMPOSITION

GRISOVIN tablets each contain 500 mg griseofulvin.

PHARMACEUTICAL FORM

Tablets.

CLINICAL PARTICULARS

Indications

GRISOVIN is indicated in the treatment of fungal infections of the skin, scalp, hair or nails caused by *Microsporum* spp., *Trichophyton* spp., *Epidermophyton* spp., where topical therapy is considered inappropriate or has failed.

Dosage and Administration

Doses should be taken after meals, otherwise absorption is likely to be inadequate.

Duration of Treatment

This depends upon the thickness of keratin at the site of infection.

For hair or skin at least four weeks treatment is required, whereas toe or finger nails may need six to twelve months treatment.

Therapy should be continued for at least two weeks after all signs of infection have disappeared.

- **Adults (greater than or equal to 50 kg)**

Normally 500 mg daily, but not less than 10 mg/kg bodyweight daily. A single dose daily is often satisfactory, but divided doses may be more effective in patients who respond poorly.

- **Children**

The 500 mg tablet is not appropriate for use in children less than 50 kg.

Contraindications

- Hypersensitivity to any ingredient of the preparation.
- Porphyria.
- Severe liver disease: *GRISOVIN* may cause liver disease to deteriorate, and liver function should be monitored in such conditions.
- Systemic lupus erythematosus: *GRISOVIN* has been reported to exacerbate the condition.
- There is no evidence of the safety of *GRISOVIN* in human pregnancy.
- Griseofulvin is teratogenic in animals and some case reports of human foetal abnormalities have been observed. Therefore, *GRISOVIN* should not be used in pregnancy, or in women intending to become pregnant within one month following cessation of treatment.
- Males should not father children within six months of treatment with *GRISOVIN*.
- Long term administration of high doses of griseofulvin with food has been reported to induce hepatomas in mice and thyroid tumours in rats but not hamsters. The clinical significance of these findings in man is not known. In view of these data, *GRISOVIN* should not be used prophylactically.

Warnings and Precautions

Customary hygienic measures should be adopted to minimise the risk of re-infection, and concurrent use of a topical fungicide may be helpful to minimise any spread of infective material.

While data from an epidemiology study have suggested an increased risk of breast cancer in patients receiving three or more prescriptions of griseofulvin (odds ratio = 1.59, 95% confidence interval 1.11-2.27), this finding has not been confirmed in other studies.

Interactions

Griseofulvin may decrease the blood level and hence efficacy of certain drugs, which are metabolised by cytochrome P450 3A4. These include oral contraceptives, coumarin anticoagulants and cyclosporin. Appropriate monitoring should be undertaken and dosage should be adjusted as necessary. Additional contraceptive precautions should be taken during *GRISOVIN* treatment and for a month after stopping *GRISOVIN*.

Absorption of griseofulvin is inhibited when phenobarbitone is taken concurrently.

The blood level, and hence efficacy, of griseofulvin may also be reduced as the result of concurrent administration of substances such as phenylbutazone and sedative and hypnotic drugs which induce metabolising enzymes.

Patients should be warned that an enhancement of the effects of alcohol by *GRISOVIN* has been reported.

Pregnancy and Lactation

There is no evidence of *GRISOVIN* safety in human pregnancy (*see Contraindications*). Griseofulvin administered to rats and mice during pregnancy has been associated with foetotoxicity and foetal malformations.

As griseofulvin is capable of inducing aneuploidy (abnormal segregation of chromosomes following cell division) in mammalian cells exposed to the compound *in vitro* and *in vivo*, women should be warned that they should not take the drug during pregnancy or become pregnant within one month following cessation of treatment.

Additionally, males should not father children within six months of treatment.

It is not known if griseofulvin is excreted in human milk. Safety in children of mothers who are breast-feeding has not been established.

Effects on Ability to Drive and Use Machines

In those rare cases where individuals are affected by drowsiness while taking *GRISOVIN*, they should not drive vehicles or operate machinery.

Adverse Reactions

Diarrhoea, nausea and vomiting are common adverse events.

Headache and gastric discomfort sometimes occur, but usually disappear as treatment continues.

On rare occasions urticarial reactions, skin rashes and precipitation of systemic lupus erythematosus have been reported.

Toxic epidermal necrolysis and erythema multiforme have been reported.

Significant elevations in LFTs (greater than three times the upper limit of normal) have been reported very rarely.

There have been reports of central nervous system effects e.g. confusion, dizziness, impaired co-ordination and peripheral neuropathy.

Leucopenia with neutropenia has been reported.

Photosensitivity reactions can occur on exposure to intense natural or artificial sunlight.

Drowsiness.

Overdose

Treatment is unlikely to be required in cases of acute overdosage.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

Griseofulvin is an antifungal antibiotic which is active *in vitro* against common dermatophytes. It exerts its antifungal effect by disrupting the cell division spindle apparatus of fungal cells, thereby arresting cell division.

Pharmacodynamic Effects

When griseofulvin is given orally for systemic treatment of fungal infections, it enables newly-formed keratin of the skin, hair and nails to resist attack by the fungi. As the new keratin extends, the old infected keratin is shed.

Microbiology:

Griseofulvin is effective against the dermatophytes causing ringworm (tinea), including: *Microsporum canis*, *T. verrucosum*, *T. mentagrophytes*, *E. floccosum* and *T. rubrum*.

Griseofulvin is not effective in infections caused by *Candida albicans* (monilia), aspergilli, *Malassezia furfur* (*Pityriasis versicolor*) and *Nocardia* species.

Pharmacokinetics

Absorption

The absorption of griseofulvin from the gastrointestinal tract is variable and incomplete. On average, less than 50% of the oral dose is absorbed, but fatty foods and a reduction in particle size will increase the rate and extent of the absorption.

After oral dosing there is a phase of rapid absorption followed by slower prolonged absorption. Peak plasma levels (0.5 to 1.5 micrograms after a 500 mg oral dose) are achieved by 4 h and are maintained for 10 to 20 h.

Distribution

In plasma griseofulvin is approximately 84% bound to plasma proteins, predominantly albumin.

There is selective deposition of griseofulvin in newly-formed keratin of hair, nails and skin, which gradually moves to the surface of these appendages.

Metabolism

6 - desmethylgriseofulvin or its glucuronide conjugate are metabolites of griseofulvin.

Elimination

The absorbed griseofulvin is excreted in the urine mainly as 6 - desmethylgriseofulvin or its glucuronide conjugate. The terminal plasma half-life ranges from 9.5 to 21 h, there being considerable intersubject variability.

Pre-clinical Safety Data

Genotoxic Potential:

The mode of action of griseofulvin as a fungicide is to interfere with microtubule assembly; this also has the potential for disruption of the cell division spindle apparatus. This disruption can lead to abnormal chromosome segregation at cell division. *In vitro* and *in vivo* genotoxicity studies have demonstrated that griseofulvin causes structural and numerical chromosome aberrations, including aneuploidy.

Carcinogenic Potential:

Long-term administration of griseofulvin showed no carcinogenic potential in the hamster but induced hepatomas in mice and thyroid tumours in rats. Both of these tumour types are considered to be induced by species specific mechanisms and therefore are thought not to represent a carcinogenic risk to humans.

PHARMACEUTICAL PARTICULARS

List of Excipients

Maize Starch, Pregelatinised Maize Starch, Povidone K 30, Sodium Lauryl Sulphate, Magnesium Stearate.

Incompatibilities

None.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

No special precautions for storage.

Nature and Contents of Container

As registered locally.

Instructions for Use/Handling

No special precautions for use and handling.

Not all presentations are available in every country.

Version number: GDS**12**/IPI**02**

Date of issue: 17 December 2009

GRISOVIN is a trademark of the GlaxoSmithKline group of companies

Manufactured and Marketed by

GaxoSmithKline Bangladesh Limited
Fouzderhat, Chittagon