PRODUCT LITERATURE

FULVICIDE TABLET 500 MG
Each tablet contains:
Griseofulvin 500 mg

Description
White coloured double scored round odourless tablet with T embossed on one side.

Pharmacodynamics
Pharmacotherapeutic group: Antifungals for systemic use.
Griseofulvin is an antifungal antibiotic that is active in vivo against common dermatophytes. The antifungal effect is manifested by binding to tubulin, at distinct binding sites, thus interferring with the microtubule function and causing inhibition of mitosis, and arresting cell division.
The inhibition of fungal mitosis leads to the production of multinucleate cells of characteristic morphology.
On entering the systemic circulation, griseofulvin binds to keratin in keratin precursor cells, thereby making them resistant to fungal infections. The drug only reaches the site of action when hair or skin is replaced by the keratin-griseofulvin complex.
Griseofulvin then enters the dermatophyte through energy dependent transport processes and binds to the fungal microtubules, interferring with, and inhibiting mitosis, and the deposition of fungal cell walls.
Mycology:
Griseofulvin has antifungal activity against the following dermatophytes, although there is species and strain variability in susceptibility.
Trichophyton rubrum, T. tonsurans, T. mentagrophytes, T. interdigitalis, T. verrucosum, T. megnini, T. gallinae,T. Crateriform, T. sulphureum and T. schoenleinii. Microsporum audouinii, M. Canis, M. gypseum. Epidermophyton floccosum.
Griseofulvin has no activity against dermatophyte fungi of other genera, non-dermatophyte fungi, yeasts, gram positive bacteria, or gram negative bacteria. If any of these are cofactors in the pathology of infection, suitable additional therapy will be required for their eradication.

Pharmacokinetics
Absorption:
The absorption of griseofulvin from the gastrointestinal tract is varaible and incomplete. On average, less than 50% of the oral dose is absorbed, but administration after a fatty meal and a reduction in particle size will increase the rate and extent of the absorption.
Following oral administration there is a phase of rapid absorption, and thereafter a phase of slower prolonged absorption.
Peak plasma levels, 0.5 µg / ml-1.5 µg / ml after a 500 mg dose, and 1.5 µg / ml-3.0 µg / ml after a 1000 mg dose, are reached in 2-4 hours, and are maintained for some 10-20 hours.
Griseofulvin exhibits linear pharmacokinetics.

Distribution:
The volume of distribution is about 0.7 L / Kg, and griseofulvin is ca 80 % bound to plasma proteins, predominantly serum albumin.
Griseofulvin crosses the placenta, and may be excreted in breast milk. There is selective deposition of griseofulvin in newly formed keratin of hair, skin, and nails, which gradually moves to the surface of these appendages.

Metabolism:
Griseofulvin undergoes metabolism to inactive metabolites, principally 6-desmethylgriseofulvin, or its glucuronide conjugate.

Excretion:
The terminal plasma half-life ranges from 9.5-21 hours, with considerable intersubject variability. The majority of the dose, as 6-desmethylgriseofulvin or the glucuronide conjugate, and other metabolites is excreted in the urine, with less than 1% administered dose being excreted as unchanged griseofulvin. The remainder of the dose, principally as metabolites, is excreted in bile and faeces.
Renal insufficiency does not lead to accumulation.

Indication
Treatment of fungal infection caused by organisms susceptible to griseofulvin.

Route of administration
Oral

Recommended Dosage
Adult : 1 tablet daily
Children above 23 kg: 1/2 - 1 tablet daily

Contraindication
Griseofulvin is contraindicated in patients who have:
- Hypersensitivity to griseofulvin or to any of the excipients
- Porphyria
- Severe hepatic impairment
- Systemic Lupus Erythematosus (SLE)
- Pregnancy
- Breastfeeding

Warning and Precautions
Griseofulvin is recommended after a high fat meal for increased absorption and minimising GI distress.
Griseofulvin is contraindicated in patients with severe hepatic impairment. In patients with minor to moderate hepatic impairment, griseofulvin may cause further deterioration of hepatic function. Therefore care should be exercised with such patients, and it is recommended to perform regular periodic liver function tests.
Griseofulvin is contraindicated in patients with Systemic Lupus Erythematosus (SLE), griseofulvin has been reported to exacerbate the conditions, and care should be taken to exclude patients with pre-existing SLE from therapy.
Animal data, indicates long term administration of high dose griseofulvin induces tumours in some species, but not others.
The clinical relevance of this to man is unknown, but griseofulvin should not be used prophylactically.
Griseofulvin is a liver microsomal enzyme inducer and thus may impair the effectiveness of oral contraceptives. Therefore in women of child bearing age using oral contraception, additional barrier methods of contraception must be used during therapy and for 4 weeks following therapy cessation.
Griseofulvin causes chromosomal abnormalities in animals. Therefore sexually active males should be cautioned to use an effective barrier method of contraception throughout therapy and for 6 months after therapy termination.
A theoretical possibility of cross sensitivity in patients known to be allergic to penicillins exists; therefore caution should be exercised in administration of griseofulvin to such patients. It should be noted that such patients have been satisfactorily treated with griseofulvin without sequelae.
Patients should be cautioned to avoid excessive and unnecessary exposure to sunlight or U.V sources, including sunbeds, during griseofulvin therapy as photosensitivity reactions can occur.
Consumption of alcohol in association with griseofulvin can result in an “Antabuse” type reaction. Patients should be cautioned to avoid consumption of alcoholic beverages, and medicines containing alcohol, while undergoing Griseofulvin therapy. In patients undergoing long term griseofulvin therapy, i.e for tinea unguium, consideration should be given to periodic monitoring of blood chemistry, particularly for patients with pre-existing blood disorders, since griseofulvin may cause blood disorders.
In common with any antibiotic, therapy with griseofulvin may result in the overgrowth of non-susceptible organisms, i.e bacteria or yeasts, or non-dermatophyte fungi that are often cofactors in tinea infections, especially tinea pedis. Additional therapy is required to control or eradicate such organisms, as griseofulvin is ineffective.
Griseofulvin is not effective in infections due to Candida albicans, Aspergillus sp., MMalassezia furfur (Pittyriasis versiclor) and Nocardia sp. It has no antibacterial effects.

Interactions with Other Medicaments
Medicinal Products:
Griseofulvin may depress plasma levels, and therefore the efficacy, of concommitantly administered medicinal products that are metabolised by cytochrome. P4503A4

Interactions of Griseofulvin with other drugs:
Ciclosporin: concomittant administration may result in a reduction of ciclosporin plasma levels, necessitating a dosage adjustment. Plasma levels of ciclosporin should be monitored during grisefulvin therapy, and necessary dosage adjustments made.

Coumarin anticoagulants: The efficacy may be reduced, necessitating dosage adjustment. It is recommended that both prothrombin and INR are regularly monitored, for the duration of griseofulvin therapy, and for 8 days post therapy cessation.

Methadone: Depression of methadone plasma levels may occur during Griseofulvin therapy. Patients should be closely monitored for any loss of efficacy, or plasma levels of methadone be monitored, and corresponding dosage adjustments made.

Oral contraceptives: Efficacy of oral contraception is reduced during Griseofulvin therapy and for four weeks post therapy cessation. In view of the contraindication in pregnancy, and of the possible sequelae of male patients fathering a child during therapy, all sexually active patients should use additional barrier contraception, such as condoms, throughout griseofulvin therapy, and for four weeks (female) and 6 months (male) post therapy cessation.

Interactions of other drugs with griseofulvin:
Concurrent administration of other medicinal products that induce metabolizing enzymes may result in a reduction of griseofulvin blood plasma levels and thus efficacy. The following drugs are known to have this effect:
Barbiturates, such as phenobarbitone, Doxercalciferol, Phenylbutazone, Primidone, Other sedative and hypnotic drugs that induce metabolising enzymes.

Food: Administration of griseofulvin after food, results in increased absorption, and thus higher plasma levels. This effect is enhanced if the meal contains high fat content. Administration after food is recommended.

Alcohol: There are reports that griseofulvin enhances the central nervous system effects of alcohol. There are also reports that griseofulvin and alcohol use result in an “Antabuse” type reaction. Patients should be cautioned to avoid alcohol and all alcohol containing products while undergoing griseofulvin therapy.

Pregnancy and Lactation
Pregnancy:
There are case reports of human foetal abnormalities associated with griseofulvin.
There are no adequate and well controlled studies in man, and inadequate epidemiological data. Griseofulvin has been shown to be teratogenic and embryotoxic in mice and rats.
Griseofulvin is suspected to cause serious birth defects when administered during pregnancy.
Griseofulvin is contraindicated in pregnancy.

Women of childbearing potential have to use effective contraception during (and up to 4 weeks after) treatment in respect of effect on oral contraceptives, and contraceptive precautions.

Male-mediated effects on pregnancy
Griseofulvin has been shown to induce chromosomal aberrations in animal spermatocytes. Therefore men should take effective contraceptive precautions, i.e barrier contraception, to avoid fathering children for the duration of griseofulvin therapy, and for 6 months post therapy cessation.

Lactation:
It is unknown if griseofulvin is excreted in breast milk, but the possibility does exist.
There is inadequate data on the safety of griseofulvin in breast feeding, and the potential risk to the infant cannot be assessed, therefore griseofulvin is contraindicated in breast feeding.

Side Effects
The following frequencies are used for the description of the occurrence of undesirable effects:

Very common	Common	Uncommon	Rare	Very Rare
> 1 / 10	> 1 / 100, <1/ 10	> 1 / 1,000, < 1 / 100	> 1 / 10,000 < 1/ 1000	< 1 / 10,000

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Headache and gastric discomfort are the most common effects on starting treatment, but usually disappear as treatment is continued.

Blood and lymphatic system disorder:
Rare: leucopenia, neutropenia, anaemia-these usually resolve on therapy cessation

Nervous system disorders:
Common: headache
Uncommon: impaired co-ordination, peripheral neuropathy, confusion, dizziness, drowsiness, insomnia, irritability.

Gastrointestinal disorders:
Common: diarrhoea, vomiting, nausea, gastric discomfort
Uncommon: anorexia, taste sensation changes

Skin and subcutaneous tissue disorders:
Uncommon: toxic epidermal necrolysis, erethema multiforme, photosensitivity on exposure to intense natural or artifical sunlight.
Rare: precipitation of Systemic Lupus Eryhthematosus, bullous reactions including Lyell's syndrome, urticarial reactions, skin rashes.

Hepatobiliary disorders:
Very rare: alteration in liver function tests, with elevation to more than three times upper normal limit, intrahepatic cholecstasis, hepatitis.

Symptoms and Treatment of Overdose
Symptoms:
The likely symptoms of any overdose would be nausea, vomiting, headache, numbness and tingling, confusion, and vertigo. Urticaria or porphyria could occur.

Treatment:
There is no specific antidote to griseofulvin. Gastric lavage or the induction of emesis may be of help, if ingestion is recent. Administration of activated charcoal may also be of use. Treatment should be symptomatic and supportive. Laboratory monitoring of haemopoetic, hepatic and nephritic parameters and electrolytes is recommended.

Effects on Ability to Drive and Use Machine
No case of overdose has been reported.

Symptoms:
The likely symptoms of any overdose would be nausea, vomiting, headache, numbness and tingling, confusion, and vertigo. Urticaria or porphyria could occur.

Treatment:
There is no specific antidote to griseofulvin. Gastric lavage, or the induction of emesis may be of help, if ingestion is recent. Administration of activated charcoal may also be of use. Treatment should be symptomatic and supportive. Laboratory monitoring of haemopoetic, hepatic and nephritic parameters and electrolytes is recommended.

Packing
Packed in blister pack of 10 x 10's tablets.

Storage Conditions
Store below 30^{o}C in a dry place, protected from direct light.
Keep away from reach of children.

Expiry Date
3 years from date of manufacture

Product Registration Holder / Distributor:
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