1.3.1 PRESCRIBING INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT

GRISEOFULVIN ORAL SUSPENSION USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each 5ml contains:

Griseofulvin USP 125mg

3. PHARMACEUTICAL FORM

Oral Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Griseofulvin oral suspension is indicated for the treatment of dermatophyte infections of the skin not adequately treated by topical therapy, hair and nails, namely:

Tinea corporis
Tinea pedis
Tinea cruris
Tinea barbae
Tinea capitis
Tinea unguium when caused by one or more of the following species of fungi:

Epidermophyton floccosum
Microsporum audouinii
Microsporum canis
Microsporum gypseum
Trichophyton crateriformis
Trichophyton gallinae
Trichophyton interdigitalis
Trichophyton megnini
Trichophyton mentagrophytes
Trichophyton rubrum
Trichophyton schoenleini
Trichophyton sulphureum
Trichophyton tonsurans
Trichophyton verrucosum

Note: Prior to therapy, a dermatophyte should be identified as responsible for the infection.

Prior to initiating treatment, appropriate specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis.

Griseofulvin is not effective in the following:

Bacterial infections	Coccidioidomycosis
Candidiasis (Moniliasis)	North American Blastomycosis
Histoplasmosis	Cryptococcosis (Torulosis)
Actinomycosis	Tinea versicolor
Sporotrichosis	Nocardiosis
Chromoblastomycosis	

The use of this drug is not justified in minor or trivial dermatophyte infections which will respond to topical agents alone.

4.2 Dosage and administration:

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium – depending on rate of growth – fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis. In some forms of tinea pedis, yeasts and bacteria may be involved as well as dermatophytes. Griseofulvin will not eradicate these associated bacterial or yeast infections.

ADULTS: 0.5 g daily (125 mg q.i.d., 250 mg b.i.d., or 500 mg/day). Patients with less severe or 300 extensive infections may require less, whereas those with widespread lesions may require a starting dose of 0.75 g to 1 g/day. This may be reduced gradually to 0.5 g or less after a response has been noted. In all cases, the dosage should be individualized.

PEDIATRIC PATIENTS (older than 2 years): A dosage of 10 mg/kg daily is usually adequate (pediatric patients from 30 to 50 lb, 125 mg to 250 mg daily; pediatric patients over 50 lb, 250 mg to 500 mg daily, in divided doses). Dosage should be individualized, as with adults. Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

Safety is not established at higher doses than recommended.

4.3 Contraindications:

Griseofulvin is contraindicated in patients with porphyria or hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Griseofulvin may cause fetal harm when administered to a pregnant woman. Two published cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy, therefore, griseofulvin is contraindicated in women who are or may become pregnant during treatment. Women taking estrogen-containing oral contraceptives may be at increased risk of becoming pregnant while on griseofulvin. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Although no direct causal relationship has been established, spontaneous abortion has been reported rarely coincident with the use of griseofulvin. Note: The Maximum Recommended Human Dose (MRHD) was set at 500 mg/day for the multiple of human exposure calculations performed in this label. If higher doses than 500 mg/day were used clinically, then the multiple of human exposure would be correspondingly reduced for that dose. For example, if a 1000 mg/day dose was administered to an individual, then the multiple of human exposure would be reduced by a factor of 2.

Griseofulvin has been shown to be embryotoxic and teratogenic in pregnant rats when given at a daily oral dose of 250 mg/kg/day [4X the Maximum Recommended Human Dose (MRHD) based on Body Surface Area (BSA)]. Griseofulvin also has been shown to be embryotoxic and teratogenic in pregnant cats treated weekly with griseofulvin at doses of 500 to 1000 mg/week. There are reports of teratogenicity in a Golden Retriever when doses of 750 mg/day [1.2X the MRHD based on BSA] were administered for four weeks prior to and throughout the pregnancy, and in a study in which beagles were administered 35 mg/kg/day [1.9X the MRHD based on BSA] for intervals from one week up to the entire gestation period. Teratogenicity was also seen in mice when griseofulvin was administered in doses equivalent to 5 g/kg/day [40X the MRHD based on BSA] for 2 consecutive days at various stages of the pregnancy.

4.4 Special Warnings and Precautions for Use

Warnings:

Prophylactic Usage

Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established.

Serious Skin Reactions

Severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) and erythema multiforme have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. If severe skin reactions occur, griseofulvin should be discontinued.

Hepatotoxicity

Elevations in AST, ALT, bilirubin, and jaundice have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. Patients should be monitored for hepatic adverse events and discontinuation of griseofulvin considered if warranted

Precautions:

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hematopoietic, should be done. Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty. Lupus erythematosus, lupus-like syndromes or exacerbation of existing lupus erythematosus have been reported in patients receiving griseofulvin. Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense or prolonged natural or artificial sunlight.

4.5 Interaction with other Medicinal products and other forms of Interaction

Griseofulvin has been reported in the literature to interfere with the metabolism of various compounds. Whether this is due to a P-450 mediated enzyme induction effects on sulfurtransferase and/or glucotransferase activity, or some other mechanism is unknown.

Griseofulvin decreases the activity of warfarin-type anticoagulants, so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy.

Griseofulvin may enhance the hepatic metabolism of estrogens, including the estrogen component of oral contraceptives, thereby reducing the effectiveness of contraception and causing menstrual irregularities. Therefore, an alternate or second form of birth control may be indicated during periods of concurrent use.
Cyclosporine levels may be reduced when administered concomitantly with griseofulvin, resulting in a decrease in the pharmacologic effects of cyclosporine.

Serum salicylate concentrations may be decreased when griseofulvin is given concomitantly with salicylates.

Barbiturates usually depress griseofulvin activity by decreasing plasma levels and concomitant administration may require a dosage adjustment of the antifungal agent.

Nausea, vomiting, flushing, tachycardia, and severe hypotension have been reported following alcohol ingestion during griseofulvin therapy.

4.6 Fertility, pregnancy and lactation

Teratogenic Effects

Pregnancy Category X

Nursing Mothers

It is not known if griseofulvin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for griseofulvin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on Ability to Drive and Use Machines:

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

4.8 Undesirable Effects

There have been postmarketing reports of severe skin and hepatic adverse events associated with griseofulvin use.

When adverse reactions occur, they are most commonly of the hypersensitivity type, such as skin rashes, urticaria, and rarely, angioneurotic edema, and erythema multiforme. These may necessitate withdrawal of therapy and appropriate countermeasures. Peripheral neuropathy and paresthesias of the hands and feet have been reported and may be related to treatment duration. Most patients treated with griseofulvin for less than six months experienced improvement or resolution of their neuropathy upon withdrawal of the griseofulvin. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion, and impairment of performance of routine activities.

Proteinuria, nephrosis (sometimes associated with existing systemic lupus erythematosus), leukopenia, coagulopathy, hepatitis, elevated liver enzymes, hyperbilirubinemia, and GI bleeding have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

4.9 Overdose

There is limited experience on overdose with griseofulvin. In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties: Antifungals

ATC CODE: D01AA08; D01BA01

Mode 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.

A prominent morphological manifestation of the action of griseofulvin is the production of multinucleate cells as the drugs inhibit fungal mitosis.

Griseofulvin causes disruption of the mitotic spindle by interacting with polymerized microtubules while the effects of the drug are thus similar to those of colchicine and vinca alkaloids, its binding sites on the microtubular protein are distinct.

5.4 Pharmacokinetic Properties

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 pf rapid absorption followed by slower prolonged absorption. Peak plasma levels (0.5-1.5 micrograms after a 500mg oral dose) are achieved by 4 hours and are maintained for 10-20 hours. The terminal plasma half-life ranges from 9.5-21 hours, there being considerable intersubject variability. In plasma griseofluvin is approximately 84% bound to plasma protiens, predominantly albumin.

The absorbed griseofulvin is excreted in the urine mainly 6-desmethylgriseofulvin and its glucuronide conjugate.

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

5.3 Pre-clinical safety data:

Griseofulvin can induce aneuploidy and meiotic delay in mouse oocytes following oral administration of high doses, i.e. 250mg/kg or greater. In addition, griseofulvin caused increases in numerical and structural chromosome aberrations in mouse spermatocytes at doses of 500mg/kg and above. Aneuploidy was observed at doses of 1500mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS:

Sodium Methyl Hydroxybenzoate, Sodium propyl Hydroxybenzoate, Sodium Benzoate , Sorbic Acid, Propylene Gycol, Carmellose Sodium, Aluminium Magnesium Silicate, Sucrose, Citric Acid, Aspartame, Tween 80, Colour Caramel, Flavour Chocolate, Flavour American Icecream, Sodium Citrate, Sucralose, Purified water.

6.2 Shelf Life

36 Months

6.3 Special Precautions for Storage

Store below 30°C. Protect from light.

6.4 Nature and Contents of Container

100ml Amber Glass Bottle with 25mm ROPP Cap.

6.5 Special Precautions for Disposal and Other Handling

Not Applicable.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

None

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable