National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

ZEENAT GRISEOFULVIN SUSPENSION/GRISEOFULVIN ORAL SUSPENSION USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains:

Griseofulvin USP 125 mg

Excipients with known effect:

Sodium Methyl Hydroxybenzoate
Sodium Propyl Hydroxybenzoate
Sodium Benzoate
Sorbic Acid
Propylene Glycol
Carmellose Sodium
Aluminium Magnesium Silicate
Sucrose
Citric Acid
Aspartame
Tween 80 (Polysorbate 80)
Colour Caramel
Flavour Chocolate
Flavour Icecream
Sodium Citrate
Sucralose
Purified Water

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.

4.2 Contraindications

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.

4.3 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.

4.4 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.

4.5 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.

4.6 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.

4.7 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

4.8 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 Pharmacodynamics 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.

5.2 Pharmacokinetic properties

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 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 Preclinical 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

6.2 List of excipients

Sodium Methyl Hydroxybenzoate BP
Sodium Propyl Hydroxybenzoate BP
Sodium Benzoate BP
Sorbic Acid BP
Propylene Glycol BP
Carmellose Sodium BP
Aluminium Magnesium Silicate BP
Sucrose BP
Citric Acid BP
Aspartame USP
Tween 80 (Polysorbate 80) BP
Colour Caramel IH
Flavour Chocolate IH
Flavour Icecream IH
Sodium Citrate BP
Sucralose BP
Purified Water BP

6.3 Incompatibilities

Not known

6.4 Shelf life

36 Months

6.5 Special precautions for storage

Store in cool place. Protect from light

6.6 Nature and contents of container

100ml Amber Glass Bottle with 25mm ROPP Cap

6.7 Special precautions for disposal <and other handling>

Not Applicable

7 APPLICANT/MANUFACTURER:

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