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| | |
|---|---|
| **Brand Name : AGOFULVIN-125 TABLETS**<br>**Generic Name :** Griseofulvin Tablets BP 125 mg | 2021 |
| | |
| **Module 1** Administrative Information and Product Information<br>**1.5** Product Information | **Confidential** |

## 1.5 PRODUCT INFORMATION

### 1.5.1 Prescribing information (Summary of products characteristics)

# SUMMARY PRODUCT CHARACTERISTICS

## 1. Name of drug product:

**AGOFULVIN-125 TABLETS** (Griseofulvin Tablets BP 125 mg)

## 2. Qualitative and Quantitative Composition:

Each uncoated tablet contains: Griseofulvin BP 125 mg

## 3. Pharmaceutical form:

White coloured uncoated tablet having break line on one side of tablet and other side is plain.

## 4. Clinical particulars:

### 4.1 Therapeutic Indications:

*Dermatophytic infections of the skin, nails and hair caused by Microsporium, Trichophyton, and Epidermophyton species*

Griseofulvin is indicated in cases of moderate to severe Tinea pedis, Tineacruris, extensive Tinea corporis, Tinea marium, Tinea facei, and Tinea capitis.Response rates from open trials are reported to be 80% or better. However, onychomycosis demonstrates a 33% failure and relapse rate. The therapeutic efficacy varies with the age of the patient. In addition, documentation of cures, partial response, and demographics of the responders versus non-responders, as well as stratification organism, site of infection, and extent of disease, are not defined in the literature. Prior to the publication of comparative trials with newer agents, there was no large series accumulation that confirmed Blank's original data, although comments from a number of sources would tend to suggest that the response rates were comparable to Blank's original data.

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Studies comparing the efficacy of griseofulvin with newer imidazole compounds have demonstrated rates of response and relapses in areas where rates of success are not well documented. Overall success rates for griseofulvin were 75%; the success rate in onychomycosis was only 67%, Success rates for the imidazoles were comparable to griseofulvin and in some series the rates of response were higher than griseofulvin and the relapse rates were lower. This, however, is not a consistent finding.

**4.2 Posology and Method of Administration:**

*Adults:* 500 mg to 1g 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. 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 requires 2-6 months for skin and hair infections, 6 to 9 months for fingernails, and at least a year for toenails.

Method of administration : Oral.

**4.3 Contraindications:**

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

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients.

**4.4 Special Warnings and Precautions for Use :**

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, 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.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

*Prophylactic Usage:*

Safety and efficacy of prophylactic use of this drug has not been established.

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Reports of animal studies in the Soviet literature state that a griseofulvin preparation was found to be embryotoxic and teratogenic on oral administration to pregnant Wistar rats. Rat reproduction studies done in the United States and Great Britain were inconclusive in this regard. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Because the potential for adverse effects on the human fetus cannot be ruled out, additional contraceptive precautions should be taken during treatment with griseofulvin and for a month after termination of treatment. Greseofulvin should not be prescribed to women intending to become pregnant within one month following cessation of therapy.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this. Griseofulvin interferes with chromosomal distribution during cell division, causing aneuploidy in plant and mammalian cells. These effects have been demonstrated *in vitro* at concentrations that may be achieved in the serum with the recommended therapeutic dosage.

Since griseofulvin has demonstrated harmful effects *in vitro* on the genotype in bacteria, plants, and fungi, males should wait at least six months after completing griseofulvin therapy before fathering a child.

**4.5 Interaction with other medicinal products, and other forms of interaction:**

*Potentially hazardous interactions*

Warfarin interaction with griseofulvin has been described with normalization of the prothrombin time in patients on both drugs. Normal volunteer trails to further characterize this interaction failed to duplicate the anecdotal reports despite adequate serum concentrations of griseofulvin.

*Other significant interactions*

Food

Food and administration of fats will enhance absorption of griseofulvin.

Alcohol

There is one report of griseofulvin potentiating the effect of alcohol.

Tobacco

Cigarette smoking does not affect the metabolism or disposition of the drug.

Contraceptive medication

Intermenstrual bleeding and amenorrhea have been reported during griseofulvin therapy in patients on the contraceptive pill (n=20). This has been confirmed in four patients in whom rechallenge with the griseofulvin resulted in recurrence of the above events. Two patients became pregnant on the contraceptive pill but both were receiving sulfonamides as well as griseofulvin at the time of conception.

Phenobarbital

The interaction between Phenobarbital and griseofulvin has been shown to be owing to a decrease in bioavailability of griseofulvin because of the effect of phenobarbital on the dissolution and absorption of griseofulvin in the gut. Thus, the effect can be reversed by the administration of griseofulvin with meals or in a lipid-soluble carrier.

*Potentially useful interactions*

Griseofulvin has been demonstrated in case reports to have an anti-inflammatory activity in cases of systemic sclerosis, gout, lichen planus, eosinophilic fascitis, and the shoulder-hand syndrome.

Adjunctive interaction of griseofulvin and cimetidine has also been reported.

Several important griseofulvin drug interaction have been recognized.

*Antacids and other cations*

Early investigational trials with quinolones revealed decreased griseofulvin absorption when co-administered with magnesium-aluminum antacids. Other cations, such as calcium, iron, and probably zinc, appear to interact in a similar manner. The proposed mechanism of the interaction is chelation between metal and the 4-oxo and adjacent carboxyl groups of quinolones.

*Theophylline*

Theophylline serum concentration haven been found to be markedly elevated when co-administered with griseofulvin At dose used fro systemic infection, griseofulvin decreases theophylline clearance by approximately 30 %. It appears that quinolones inhibit specific cytochrome P450 isozymes responsible for metabolism of methylxanthlines.

*Anticoagulants*

Griseofulvin may increase the prothrombin time in patients receiving warfarin and monitoring should be performed during concomitant treatment.

*Others*

A decreased griseofulvin absorption has been observed with concurrent sucralfate administration. It is possible that rifampin may induce the metabolism of Griseofulvin, leading to lower serum concentration and failure of therapy. The combination of griseofulvin and chloramphenicol may be antagonistic. Increased creatinine may occur if patients receiving cyclosporine are given griseofulvin. Griseofulvin may potentiate the effect of glyburide if the drugs are taken simultaneously.

Potentially useful interactions

The combination of griseofulvin with an antipseudomal penicillin has been reported to be synergistic for 20 -50 % of isolates of Pseudomonas aeruginosa.

**4.6 Pregnancy and Lactation:**

*Pregnancy*

The drug should be avoided in this situation. Teratogenicity has been documented in animals but not in humans. The potential for griseofulvin to cross the placental barrier because of its lipid solubility, and its ability to arrest cells in vitro in metaphase and cause the polyploidy, preclude its use in pregnancy.

*Lactation*

The drug should be avoided in women who are breast-feeding.

**4.7 Effects on ability to drive and use machines:**

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Griseofulvin Tablets should refrain from driving or using machines.

**4.8 Undesirable effects:**

Potentially life-threatening effects

One patient has died with an exacerbation of systemic lupus erythematous on griseofulvin. Rare reports of angioedema are described.

Severe or irreversible adverse effects

Apart from those described immediately above none has been reported.

Symptomatic adverse effects

Patients have complained of severe headaches, nausea and diarrhea after the administration of griseofulvin. Other symptomatic adverse effects have been included urticaria, fixed drug eruptions, cholestasis and downgrading reactions in leprosy (from the lepromatous form to the tuberculoid form).

Other effects

No abnormalities of liver function and other abnormalities of chemistry or hematologic parameters have been noted in patients who are asymptomatic when receiving griseofulvin therapy.

**4.9 Overdose:**

The symptoms of overdosage consist of headache, skin rashes, dryness of the mouth, an altered sensation of taste, and gastrointestinal disturbances. Angioderma, 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 griseofulvin. Oral thrush, granulocytopenia or leucopenia and peripheral neuritis can also occur less frequently and in these cases the dosage should be reduced or the medicine discontinued. Treatment is supportive and symptomatic.

## 5. Pharmacological properties:

### 5.1 Pharmacodynamic properties:

Griseofulvin is fungistatic in vitro for various species of the dermatophytes Microsporum, Epidermophyton and Trichophyton. 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 microtubules.

### 5.2 Pharmacokinetic Properties:

Griseofulvin can be assayed using gas or high pressure liquid chromatography with fluorescence detection, and its metabolites can be detected using spectrophotometric methodology. The sensitivity of the preferred analytical method for drug in biological fluids is 50$\mu g.l^{-1}$.

The binding of griseofulvin to serum proteins is not reported.

The pharmacokinetics have been extensively studied and have demonstrated a volume of distribution of 1.2-1.41.$kg^{-1}$.The $\alpha$ half-life in humans has ranged from 0.7 to 1.7h with a $\beta$ half-life of 9.5-21 h after intravenous administration .The $\beta$ half-life is comparable after oral administration of the drug. The peak concentration after oral administration of griseofulvin was 0.5-2.0$mg.l^{-1}$ after a 500 mg dose.

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There appears to be extensive accumulation in the areas of infected skin and sweat. There is considerable extraction of griseofulvin from the serum into the interstitium at the microvascular level. The tissue distribution of the drug appears to be in keeping with its lipid solubility characteristics. Animal studies have demonstrated that accumulation occurs in the lungs after intravenous administration and in the liver after oral administration. Concentrations in the skin and various strata of the skin have been shown to exceed serum levels but fall rapidly after drug cessation. This can be explained by a wash-out effect as a result of drug secretion in sweat .The effect of dehydration and sweating on cutaneous concentrations of griseofulvin is dramatic and demonstrates increasing concentrations in the skin with increasing hydration status and increasing wash-out of griseofulvin with increased perspiration.

Griseofulvin is eliminated primarily by metabolic degradation which, in humans, is primarily to 6-desmethylgriseofulvin (Fig.1).Excretion of this metabolite is primarily in the urine (50%) and up to 30% is excreted in the feces .Three other metabolites account for 16% of the total drug recovery after oral administration.

Absorption of the drug orally is dependent upon the particle size of the drug formulation and solubilization in lipid carriers. Food ingestion also alters absorption of the drug. There are also intraindividual differences of absorption which result in large coefficients of variation for absorption.

The relative bioavailability can be enhanced by 120% in the presence of fats .The site of absorption appears to be the duodenum. Peak concentrations of the drug could be increased two-to threefold with the use of microcrystalline preparation and a further twofold increase could be seen with the addition of fats at the time of administration.

Kinetics of the drug in patients with hepatic and renal dysfunction have not been reported although it is likely that elimination would be impaired in hepatic disease.

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|---|---|
| Oral absorption | variable |
| Presystemic metabolism | — |
| Plasma half-life range | 9.5-21 h |
| Volume of Distribution | 1.2-1.41.l.kg$^{-1}$ |
| Plasma protein binding | — |

Concentration-effect relationship

Only one study has addressed the relationship between the plasma concentrations and therapeutic effect and it was unable to correlate clinical response with serum concentration. No studies correlating tissue concentration and clinical response have been reported.

Metabolism

Griseofulvin is metabolized extensively by the liver to 6-desmethyl griseofulvin, which is conjugated with glucuronic acid.

Minor metabolites have been described in humans and animals. These metabolites appear to be inactive and excretion via the urine is rapid .A considerable enterohepatic circulation of the metabolites occurs in animals (although variable among species) and may also occur in humans. In particular, griseofulvin affects the concentration and the functional integrity of a number of hepatic endoplasmic reticular enzymes. This is most apparent in the porphyrin metabolism. This results in the accumulation of co-proporphyrin, protoporphyrin, and hemopexin .It has been recently demonstrated that griseofulvin may inhibit protoheme ferrolyase which may account for the accumulation of the green pigment in the liver.

In addition, while griseofulvin increases the weight of mouse liver, the P450 content decreases dramatically, whereas the cytochrome $b_5$ increases substantially. The total functional capacity of the P450 system is, therefore, unchanged, and although the activity expressed on the basis of total P450 content is effectively doubled.

### 5.3 Pre-clinical safety data:

Griseofulvin has demonstrated teratogenic effects in rats at doses of 1250-1500 mg daily. Teratogenicity has also been described in cats at lower doses of 100 mg per day or less. Mutagenicity of griseofulvin has not been demonstrated. Human carcinogenicity or teratogenicity has not been demonstrated. No toxic reactions of dose-related origin have been demonstrated in humans.

Griseofulvin has limited interaction with mammalian cells. There has been evidence that griseofulvin interacts with spindle formation and metaphase; however the extent of interaction is not fully understood.

## 6. Pharmaceutical particulars:

### 6.1 List of Excipients:

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| Lactose | BP |
| Maize starch | BP |
| Sodium starch glycollate | BP |
| Colloidal silicone dioxide | BP |
| Sodium Lauryl Sulphate | BP |
| Sodium methyl paraben | BP |
| Purified talc | BP |
| Magnesium stearate | BP |
| Cross carmellose sodium | BP |
| Polyplasdone XL(Cross povidone) | BP |

### 6.2 Incompatibilities:

None Reported

**6.3 Shelf-Life:**
36 months from the date of manufacture.

**6.4 Special Precautions for Storage:**
Store in a cool, dry and dark place. Protect from light.

**6.5 Nature and Contents of Container:**
10 tablets packed in one blister. Such blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

**6.6 Special precautions for disposal:**
None reported.

## 7. Registrant:

**AGOG PHARMA LTD.**
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## 8. Manufacturer:

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## 9. Date of revision of the text :