SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGOFULVIN TABLETS (Griseofulvin Tablets BP 500 mg)

2. Qualitative and Quantitative Composition:

Each uncoated tablet contains: Griseofulvin BP 500 mg

3. Pharmaceutical form:

White coloured uncoated tablet having 'GR/'500' embossing one side and "AGOG" embossing other side.

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.

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.

Oral administration of griseofulvin for systemic therapy of fungal infections enables newly formed keratin of the skin, hair, and nails to resist fungal attack. As the new keratin extends, the old infected keratin is shed.

Prior to therapy, the type of fungi responsible should be identified. The use of griseofulvin is not justified in the treatment of minor or trivial infections that will respond to topical therapy.

Before prescribing Griseofulvin Tablets, consideration should be given to national and/or local guidance on the appropriate use of antifungals.

4.2 Posology and Method of Administration:

For oral administration.

Tablets should be swallowed whole with a glass of water. Griseofulvin is recommended to be taken after a high fat meal, for increased absorption and minimising GI distress, see section 5.2.

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 tine pedis, yeasts and bacteria may be involved as well as fungi. Griseofulvin will not eradicate the bacterial or candidal infections.

Adults

The usual adult dose is 500 mg to 1000 mg daily. The dose should not be less than 10 mg / Kg bodyweight / day. The dose may be administered as a single daily dose, or it may be administered twice daily. The twice daily dosing regimen may be more effective in those patients who respond poorly.

Hepatic impairment

Griseofulvin is contraindicated in patients with severe hepatic impairment, see section 4.3.

For patients with moderate to mild hepatic impairment, no dosage adjustment is required. However, griseofulvin may lead to further impairment of hepatic function, therefore regular monitoring of liver function is mandated, see section 4.4.

Renal impairment

No dosage adjustment is required in renally impaired patients; renal insufficiency does not lead to accumulation.

Elderly

No dosage adjustment is required in the elderly. Consideration should be given that such patients may also have a degree of hepatic impairment, see section 4.4.

Children

The dosage form, film-coated tablet, is only suitable for children of an age to swallow the tablet.

The usual dose in 10 mg / Kg bodyweight / day, in divided doses.

Duration of therapy

The duration of theapy depends upon the thickness of keratin at the site of infection, and the clinical response. The following duration of therapy are indicative:

Tinea corporis: 2-4 weeks

Tinea capitis: 4-8 weeks, in refractory cases, 8-12 weeks

Tinea pedis: 4-8 weeks

Tinea unguium: 6-12 months

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

Method of administration: Oral.

4.3 Contraindications:

Griseofulvin is contraindicated in patients who have:

- Hypersensitivity to griseofulvin or to any of the excipients, see section 6.1
- Porphyria
- Severe hepatic impairment
- Systemic Lupus Erythematosus (SLE)
- Pregnancy, see section 4.6
- Breastfeeding, see section 4.6

4.4 Special Warnings and Precautions for Use:

Griseofulvin is recommended after a high fat meal for increased absorption and minimising GI distress.

Griseofulvin is contraindicated in patients with severe hepatic impairment, see section 4.3. 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, see section 4.8.

Griseofulvin is contraindicated in patients with Systemic Lupus Erythematosus (SLE), see section 4.3; griseofulvin has been reported to exacerbate the conditions, and care should be taken to exclude patients with pre-existing SLE from therapy.

Animal data, see section 5.3, 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, see sections 4.5 and 4.6.

Griseofulvin causes chromosomal abnormalities in animals, see section 5.3. Therefore, sexually active males should be cautioned to use an effective barrier method of contraception throughout therapy and for 6 months after therapy termination, see section 4.6.

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, see section 4.8.

Consumption of alcohol in association with griseofulvin can result in an “Antabuse” type reaction, see section 4.5. 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, see section 4.8.

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.

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

Medicinal Products:

Griseofulvin may depress plasma levels, and therefore the efficacy, of concommitantly administered medicinal products that are metabolised by cytochrome P450 3A4.

Interactions of Griseofulvin with other drugs:

Ciclosporin: concomitant administration may result in a reduction of ciclosporin plasma levels, necessitating a dosage adjustment. Plasma levels of ciclosporin should be monitored during griseofulvin 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, see section 4.3, 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. See also sections 4.3, 4.4, 4.6, and 5.3 for additional information.

Interactions of other drugs with griseofulvin:

Concurrent administration of other medicinal products that induce metabolising 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, see section 4.2.

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, See also section 4.8.

4.6 Pregnancy and Lactation:

Pregnancy:

There is 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. (see section 5.3).

Griseofulvin is suspected to cause serious birth defects when administered during pregnancy.

Griseofulvin is contraindicated (see section 4.3) in pregnancy.

Women of childbearing potential have to use effective contraception during (and up to 4 weeks after) treatment (see section 4.5) 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 (see section 5.3). 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 (see section 4.3).

4.7 Effects on ability to drive and use machines:

Griseofulvin has no or negligible influence on the ability to drive and use machines. However, it may cause drowsiness, confusion dizziness, and impaired co-ordination, see section 4.8. Patients should therefore be cautioned not to drive or operate machines until they are sure they are not affected.

4.8 Undesirable effects:

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

Very common:	≥ 1 / 10
Common:	≥ 1 / 100, < 1 / 10
Uncommon:	≥ 1 / 1,000, < 1 / 100
Rare:	≥ 1 / 10,000, < 1 / 1,000
Very rare:	< 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, erythema multiforme, photosensitivity on exposure to intense natural or artificial 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.

4.9 Overdose:

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.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antifungals for systemic use

ATC code: D01BA01

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.

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 50μg.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 α half-life in humans has ranged from 0.7 to 1.7h with a β half-life of 9.5-21 h after intravenous administration .The β 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.
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.

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 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 1500 mg/kg.

Griseofulvin administered to rats and mice during pregnancy has been associated with foetotoxicity and foetal malformations. 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 (see contraindications). The effects in mice may be due to a species specific effect on porphyrin metabolism.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactose	BP
Maize starch	BP
Sodium starch glycollate	BP
Colloidal silicone dioxide	BP
Sodium Lauryl Sulphate	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 under normal storage condition (15˚C- 30˚C).
Protect from light.
Keep all medicines out of reach of children.

6.5 Nature and Contents of Container:

10 tablets packed in one Alu/PVC blisters. 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.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane,
India.

8. Marketing authorisation number

TAN 22 HM 0333

9. Date of first authorisation/renewal of the authorisation

21/09/2022

10. Date of revision of the text