1.3.1 Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

1.1 (Invented) Name of the Medicinal Product

Griseofulvin Tablets 500mg

1.2 Strength

Griseofulvin 500mg

1.3 Pharmaceutical Form

Oral Solid Dosage Form, Tablet

2. Qualitative and quantitative composition

griseofulvin USP Eq to Griseofulvin 500mg

Excipients.....

No.	Ingredients	Quantity	
		100,000 Tablets	
1	Griseofulvin	500mg	50KG
2	Starch	96mg	9.6 KG
3	Sucrose	32mg	3.2KG
4	Dextrin	32mg	3.2 KG
5	Magnesium stearate	16mg	1.6kg
6	Sodium Starch Glycolate	40mg	4 kg
7	K30	48mg	4.8kg

3. Pharmaceutical form

White or almost white tablet.

4. Clinical particulars

4.1 Therapeutic indications

➢ Ultramicrosize griseofulvin tablets are indicated for the treatment of the following ringworm infections;

➢ tinea corporis (ringworm of the body),

➢ tinea pedis (athlete's foot),

➢ tinea cruris (ringworm of the groin and thigh),

➢ tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails), when caused by one or more fungi

4.2 Posology and method of administration

Posology

General: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. 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 candidial 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 therapy 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.

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

Commended after a high fat meal for increased absorption and minimizing 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: 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, 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 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. (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, 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.

4.9 Overdose

No case of overdose has been reported.

Symptoms:

The likely symptoms of any overdose would be nausea, nomiting, 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

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 beinge 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.

6. Pharmaceutical particulars

6.1 List of excipients

Starch
Sucrose
Dextrin
Magnesium stearate
Sodium starch glycolate
Povidone

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C. in a dry place, protected from light.

6.5 Nature and contents of container

Tablets filled in blister (hard PVC and aluminum foil) then packed in carton along with Package insert.

6.6 Special precautions for disposal

No special requirements

7. Registrant

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