**GRISEOFULVIN (Systemic)**

Introduction

Revised: 08/08/2000

VA CLASSIFICATION (Primary)¾AM700

Commonly used brand name(s):Fulvicin P/G; Fulvicin U/F; Fulvicin-U/F; Grifulvin V; Gris-PEG; Grisactin; Grisactin Ultra.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antifungal (systemic).

Indications

Accepted

Tinea barbae (treatment)

Tinea capitis (treatment)

Tinea corporis (treatment)

Tinea cruris (treatment)

Tinea pedis (treatment) or

Tinea unguium¾Griseofulvin is indicated in the treatment of tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis, and tinea unguium (onychomycosis) caused by Trichophyton rubrum , T. tonsurans , T. mentagrophytes , T. interdigitale , T. verrucosum , T. megninii , T. gallinae , T. schoenleinii , Microsporum audouinii , M. canis , M. gypseum , and Epidermophyton floccosum. 17, 18

Not all species or strains of a particular organism may be susceptible to griseofulvin. In addition, griseofulvin may not be effective because of poor absorption or inadequate tissue concentrations of griseofulvin.

Unaccepted

Griseofulvin is not indicated in the treatment of minor or trivial infections that will respond to topical antifungals alone. 17, 18

Griseofulvin is not effective in the treatment of bacterial infections, candidiasis, histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis, tinea versicolor, or nocardiosis. 3, 17, 18

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾352.77 19

Mechanism of action/Effect:

Fungistatic 23 ; griseofulvin inhibits fungal cell mitosis by causing disruption of the mitotic spindle structure, thereby arresting the metaphase of cell division. It is deposited in varying concentrations in the keratin precursor cells of skin, hair, and nails, rendering the keratin resistant to fungal invasion. As the infected keratin is shed, it is replaced with healthy tissue. 8, 17

Absorption:

Microsize¾Variable, ranging from 25 to 70% of an oral dose.

Ultramicrosize¾Almost completely absorbed.

Absorption is significantly enhanced by administration with or after a fatty meal. 3, 11

Distribution:

Griseofulvin is deposited in varying concentrations 8 in the keratin layer of the skin, hair, and nails. It can be detected in the stratum corneum of the skin 22 within a few hours following administration. Only a very small fraction of an oral dose is distributed in the body fluids and tissues.

Biotransformation:

Hepatic; major metabolites are 6-methyl-griseofulvin and its glucuronide conjugate. 22, 23

Half-life:

Approximately 24 hours. 21

Time to peak serum concentration

Approximately 4 hours following administration of a single dose of 250 mg of ultramicrosize griseofulvin or 500 mg of microsize griseofulvin. 11, 12

Elimination:

Renal. Less than 1% of a dose is excreted as unchanged drug in the urine. Approximately 36% of griseofulvin is excreted unchanged in the feces. 23

Precautions to Consider

Cross-sensitivity and/or related problems

Since griseofulvin is derived from a species of Penicillium , it is theoretically possible that patients intolerant of penicillins or penicillamine may be intolerant of griseofulvin also. However, cross-sensitivity between griseofulvin and penicillins or penicillamine has not been clinically substantiated. In addition, penicillin-sensitive patients have received griseofulvin without difficulty. 5, 12

Carcinogenicity/Tumorigenicity/Mutagenicity

Griseofulvin has been shown to cause hepatomas in several strains of mice, particularly males, that were chronically fed griseofulvin at levels ranging from 0.5% to 2.5% of their diet. Smaller particle-size griseofulvin resulted in an enhanced tumorigenic effect. Griseofulvin, given subcutaneously in relatively small doses once a week during the first 3 weeks of life, has also been shown to cause hepatomas in mice. 11

Griseofulvin has been shown to cause thyroid tumors, mostly adenomas but also some carcinomas, in male rats that were fed griseofulvin at levels of 0.2%, 1%, and 2% of their diet. Thyroid tumors were also reported in female rats that were fed the two higher dosage levels of griseofulvin. 11

Studies in other animal species have not shown that griseofulvin is tumorigenic, however. 11

Griseofulvin has been shown to have a colchicine-like effect on mitosis and to be cocarcinogenic with methylcholanthrene in cutaneous tumor induction studies in laboratory animals. 5, 11

Pregnancy/Reproduction

Fertility¾Griseofulvin has been shown to suppress spermatogenesis in rats, although this has not been confirmed in humans. 5

Pregnancy¾Griseofulvin crosses the placenta. Conjoined twins have been reported rarely in patients taking griseofulvin during the first trimester of pregnancy. Therefore, this medication is not recommended for use during pregnancy.

Studies in rats have shown that griseofulvin is embryotoxic and teratogenic. In addition, studies in dogs have shown that griseofulvin may cause adverse effects in pups. 5, 17

Breast-feeding

It is not known whether griseofulvin is excreted in breast milk. However, problems in humans have not been documented.

Pediatrics

Appropriate studies on the relationship of age to the effects of griseofulvin have not been performed in children up to 2 years of age. 17

Geriatrics

Appropriate studies on the relationship of age to the effects of griseofulvin have not been performed in the geriatric population. However, no geriatrics-specific problems have been documented to date.

Dental

Griseofulvin may cause oral thrush (soreness or irritation of mouth or tongue). 12

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>>  = major clinical significance):

Note:  Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Alcohol 4, 12

(effects may be potentiated when alcohol is used concurrently with griseofulvin; also, concurrent use with griseofulvin may result in tachycardia, diaphoresis, and flushing)

>>  Anticoagulants, coumarin- or indandione-derivative 12, 28

(anticoagulant effects may be decreased when these agents are used concurrently with griseofulvin; decrease is thought to be due to accelerated metabolism of anticoagulants secondary to stimulation of hepatic microsomal enzyme activity; prothrombin time should be monitored until a stable level is maintained; dosage adjustments may be necessary during and after griseofulvin therapy)

Barbiturates or

Primidone 27

(antifungal effects of griseofulvin may be decreased when it is used concurrently with primidone or barbiturates, especially phenobarbital, because of impaired absorption, resulting in decreased serum concentrations; although the effect of decreased serum concentrations on therapeutic response has not been established, concurrent use is preferably avoided)

>>  Contraceptives, estrogen-containing, oral 2, 29, 30, 31

(concurrent long-term use of griseofulvin may decrease the effectiveness of oral contraceptives, possibly because of stimulation of hepatic microsomal enzyme activity, resulting in decreased serum estrogen concentrations; this may lead to intermenstrual bleeding, amenorrhea, or unplanned pregnancies; patients should be advised to use an alternate or additional method of contraception

while taking griseofulvin concurrently with estrogen-containing oral contraceptives and for 1 month after stopping griseofulvin)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist

>> Hepatic dysfunction 13

(griseofulvin may on rare occasion be hepatotoxic)

Hypersensitivity to griseofulvin

Lupus erythematosus or lupus-like syndromes

(griseofulvin may precipitate or exacerbate lupus 5, 12 )

>> Porphyria 13, 26

(griseofulvin may precipitate porphyria attacks)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Complete blood count (CBC) and

Creatinine concentration, serum and

Hepatic function determinations

(recommended at periodic intervals during therapy 12 )

Urinalysis

(recommended at periodic intervals during therapy since proteinuria has been rarely reported 12 )

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence less frequent 12, 13

Confusion; hypersensitivity (skin rash, hives, or itching); oral thrush (soreness or irritation of mouth or tongue); photosensitivity (increased sensitivity of skin to sunlight)

Incidence rare¾more frequent with prolonged use and/or high doses 12, 13Granulocytopenia or leukopenia (sore throat and fever); hepatitis (yellow eyes or skin); peripheral neuritis (numbness, tingling, pain, or weakness in hands or feet)

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent 12, 13

Headache

Incidence less frequent 12, 13

Dizziness; gastrointestinal reactions (diarrhea; nausea or vomiting; stomach pain); insomnia (trouble in sleeping); unusual tiredness

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Griseofulvin (Systemic).

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to griseofulvin; theoretic cross-sensitivity with penicillin, however, penicillin-sensitive patients have received griseofulvin without difficulty

Pregnancy¾Griseofulvin crosses the placenta; use is not recommended during pregnancy since griseofulvin has been shown to be embryotoxic and teratogenic in rats

Dental¾Griseofulvin may cause oral thrush

Other medications, especially coumarin- or indandione-derivative anticoagulants or estrogen-containing oral contraceptives

Other medical problems, especially hepatic dysfunction or porphyria

Proper use of this medication

>> Taking with or after meals, especially fatty ones, to minimize gastrointestinal irritation and to increase absorption; checking with physician if on low-fat diet

Proper administration technique for oral suspension

>> Compliance with full course of therapy

>> Proper dosing

Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses

>> Proper storage

Precautions while using this medication

Regular visits to physician to check progress during therapy

>> Use of an alternate or additional means of contraception if taking estrogen-containing oral contraceptives concurrently and for 1 month after stopping griseofulvin

Caution in drinking alcoholic beverages during griseofulvin therapy

>> Caution if dizziness occurs

>> Possible photosensitivity reactions

Side/adverse effects

Signs of potential side effects, especially confusion, hypersensitivity, photosensitivity, oral thrush, granulocytopenia, leukopenia, and peripheral neuritis

General Dosing Information

An oral dose of 250 to 330 mg of ultramicrosize griseofulvin [3, 17, 23, 25] produces serum concentrations equal to 500 mg of microsize griseofulvin.

Griseofulvin should be administered with or after meals (preferably meals high in fat content) to minimize possible gastrointestinal irritation and to increase absorption. [11]

To help prevent relapse, therapy should be continued until the infecting organism is completely eradicated as determined by clinical or laboratory examination. Representative treatment periods are: tinea capitis, 8 to 10 weeks [7, 32]; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; onychomycosis, at least 4 months for fingernails and at least 6 months for toenails. However, recurrence rates in the treatment of onychomycosis of the toenails are very high. [4, 17]

Concurrent use of an appropriate topical agent is usually required, particularly in the treatment of tinea pedis, since both yeasts and bacteria as well as fungi may be involved in some forms of

athlete's foot. Also, griseofulvin is not effective against bacterial or monilial infections. In addition, concurrent use with a topical antifungal agent may reduce the likelihood of relapse. 3

Oral Dosage Forms

GRISEOFULVIN CAPSULES (MICROSIZE) USP

Usual adult and adolescent dose

Antifungal¾Onychomycosis; or

Tinea pedis: Oral, 500 mg every twelve hours. 4

Tinea barbae

Tinea capitis

Tinea corporis

Tinea cruris

: Oral, 250 mg every twelve hours; or 500 mg once a day. 4, 10

Usual pediatric dose

Antifungal¾Oral, 5 mg per kg of body weight or 150 mg per square meter of body surface every twelve hours; or 10 mg per kg of body weight or 300 mg per square meter of body surface once a day; 4, 10 or for

Children 14 to 23 kg: Oral, 62.5 to 125 mg every twelve hours; or 125 to 250 mg once a day. 4, 10

Children 23 kg and over: Oral, 125 to 250 mg every twelve hours; or 250 to 500 mg once a day. 4, 10

Strength(s) usually available

U.S.¾250 mg (Rx)[Grisactin]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· May cause dizziness.

· Avoid alcoholic beverages.
· Avoid too much sun or use of sunlamp.
· Continue medicine for full time of treatment.
· Take with or after meals or milk.

GRISEOFULVIN ORAL SUSPENSION (MICROSIZE) USP

Usual adult and adolescent dose

See Griseofulvin Capsules USP (Microsize) .

Usual pediatric dose

See Griseofulvin Capsules USP (Microsize) .

Strength(s) usually available

U.S.¾125 mg per 5 mL (Rx)[Grifulvin V (alcohol 0.008%) (methylparaben) (propylparaben)]

Canada¾Not commercially available.

Packaging and storage:

Store at room temperature. 37 Store in a tight container. Protect from freezing.

Auxiliary labeling:

· Shake well.
· May cause dizziness.
· Avoid alcoholic beverages.
· Avoid too much sun or use of sunlamp.
· Continue medicine for full time of treatment.
· Take with or after meals or milk.

Note: When dispensing, include a calibrated liquid-measuring device.

GRISEOFULVIN TABLETS (MICROSIZE) USP

Usual adult and adolescent dose

See Griseofulvin Capsules USP (Microsize).

Usual pediatric dose

See Griseofulvin Capsules USP (Microsize).

Strength(s) usually available

U.S.¾250 mg (Rx)[Fulvicin-U/F (scored)] [Grifulvin V (scored)]

500 mg (Rx)[Fulvicin-U/F (scored)] [Grifulvin V (scored)] [Grisactin]

Canada¾500 mg (Rx)[Fulvicin U/F (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· May cause dizziness.
· Avoid alcoholic beverages.
· Avoid too much sun or use of sunlamp.
· Continue medicine for full time of treatment.
· Take with or after meals or milk.

ULTRAMICROSIZE GRISEOFULVIN TABLETS USP

Usual adult and adolescent dose

Antifungal¾Onychomycosis or

Tinea pedis: Oral, 250 to 375 mg every twelve hours. 4, 6

Tinea barbae

Tinea capitis

Tinea corporis or

Tinea cruris: Oral, 125 to 187.5 mg every twelve hours; or 250 to 375 mg once a day. 4, 6

Usual pediatric dose

Antifungal¾Oral, 2.75 to 3.65 mg per kg of body weight every twelve hours; or 5.5 to 7.3 mg per kg of body weight once a day; 4 or for

Children 14 to 23 kg: Oral, 31.25 to 82.5 mg every twelve hours; or 62.5 to 165 mg once a day. 4

Children 23 kg and over: Oral, 62.5 to 165 mg every twelve hours; or 125 to 330 mg once a day. 4

Note:  Infants and children up to 2 years of age¾Dosage has not been established. 5,  6

Strength(s) usually available

U.S.¾100 mg (Rx)

125 mg (Rx)[Fulvicin P/G (scored)] [Gris-PEG (scored) (methylparaben )]

165 mg (Rx)[Fulvicin P/G (scored)]

250 mg (Rx)[Fulvicin P/G (scored)] [Grisactin Ultra (scored)] [Gris-PEG (scored) (methylparaben)]

330 mg (Rx)[Fulvicin P/G (scored)] [Grisactin Ultra (scored)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Ultramicrosize griseofulvin 165 mg and 330 mg tablets can be stored between 2° and 30° Celsius (36° and 86° F). 35, 36 Store in a well-closed container.

Auxiliary labeling:

- May cause dizziness.
- Avoid alcoholic beverages.
- Avoid too much sun or use of sunlamp.
- Continue medicine for full time of treatment.
- Take with or after meals or milk.