62483/S5

S-005

Date Approved: May 28, 1987

ORTHO

ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869-0602

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
MAY 22 1987

Antibiotic Drug Review Branch
Division of Generic Drugs, #16B-11
Center for Drugs & Biologics
5600 Fishers Lane
Rockville, MD 20857

Special Supplement - Changes Being Effected

NDA 62-279
NDA 62-483
GRIFULVIN V® (griseofulvin microsize) Tablets and Suspension

Gentlemen:

Reference is made to the subject approved antibiotic applications and, specifically, to your letter of February 26, 1987 (copy attached) requesting the following revisions in the package insert that is used in common for these products:

a) Deletion of the "Usage in Pregnancy" statement from the WARNINGS section.

b) Addition of a statement to indicate that the drug is contraindicated in pregnancy.

Attached herewith are 12 copies of the printed package insert (4 mounted and 8 unmounted) which has been revised by means of the requested deletion and by the addition of the requested contraindication to its CONTRAINDICATIONS Section, using the text proposed for it in your letter.

This revised package insert will be put into use immediately.

For your convenience, we are attaching a duplicate set of this communication and attachments to be used for the second NDA referenced above.

Very truly yours,

ORTHO PHARMACEUTICAL CORPORATION

A. J. Vazakas

A. J. Vazakas, Ph.D.
Manager of Regulatory Affairs

AJV/lm
0273
attachment

23740

RECEIVED MAY 27 1987

631-10-560-5

Grifulvin V

(griseofulvin microsize)

Tablets / Suspension

Orally effective antifungal agent for ringworm infections of the hair, skin, and nails

Improved absorption – Higher blood levels

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869
a Johnson & Johnson Company

Description

Griseofulvin is an antibiotic derived from a species of *Penicillium*. Each GRIFULVIN V Tablet contains either 250 mg or 500 mg of griseofulvin microsize, and also contains calcium stearate, colloidal silicon dioxide, starch, and wheat gluten. Additionally, the 250 mg tablet also contains dibasic calcium phosphate. Each 5 ml of GRIFULVIN V Suspension contains 125 mg of griseofulvin microsize and also contains alcohol 0.008%, docusate sodium, FD&C Red No. 40, FD&C Yellow No. 6, flavors, magnesium aluminum silicate, menthol, methylparaben, propylene glycol, propylparaben, saccharin sodium, simethicone emulsion, sodium alginate, sucrose, and purified water.

Clinical Pharmacology

GRIFULVIN V (griseofulvin microsize) acts systemically to inhibit the growth of Trichophyton, Microsporum, and Epidermophyton genera of fungi. Fungistatic amounts are deposited in the keratin, which is gradually exfoliated and replaced by noninfected tissue.

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals, mainly because of insolubility of the drug in aqueous media of the upper G.I. tract. The peak serum level found in fasting adults given 0.5 gm. occurs at about four hours and ranges between 0.5 and 2.0 mcg./ml.

It should be noted that some individuals are consistently "poor absorbers" and tend to attain lower blood levels at all times. This may explain unsatisfactory therapeutic results in some patients. Better blood levels can probably be attained in most patients if the tablets are administered after a meal with a high fat content.

Indications and Usage

Major indications for GRIFULVIN V (griseofulvin microsize) are:

- Tinea capitis (ringworm of the scalp)
- Tinea corporis (ringworm of the body)
- Tinea pedis (athlete's foot)
- Tinea unguium (onychomycosis; ringworm of the nails)
- Tinea cruris (ringworm of the thigh)
- Tinea barbae (barber's itch)

GRIFULVIN V (griseofulvin microsize) inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, skin, and nails, such as:

- Trichophyton rubrum
- Trichophyton tonsurans
- Trichophyton mentagrophytes
- Trichophyton interdigitalis
- Trichophyton verrucosum
- Trichophyton sulphureum
- Trichophyton schoenleini
- Microsporum audouini
- Microsporum canis

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Trichophyton verrucosum
Trichophyton sulphureum
Trichophyton schoenleini
Microsporum audouini
Microsporum canis
Microsporum gypseum
Epidermophyton floccosum
Trichophyton megnini
Trichophyton gallinae
Trichophyton crateriform

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical antifungal agents alone.

It is *not* effective in:

Bacterial infections
Candidiasis (Moniliasis)
Histoplasmosis
Actinomycosis
Sporotrichosis
Chromoblastomycosis
Coccidioidomycosis
North American Blastomycosis
Cryptococcosis (Torulosis)
Tinea versicolor
Nocardiosis

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.

Warnings

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 thus far in the United States and Great Britain have been inconclusive in this regard, and additional animal reproduction studies are underway. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this.

Precautions

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.

Drug Interactions: Patients on warfarin-type anticoagulant therapy may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Concomitant use of barbiturates usually depresses griseofulvin activity and may necessitate raising the dosage.

The concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives and to increase the incidence of breakthrough bleeding.

Adverse Reactions

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. 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 and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

Dosage and Administration

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium – depending on rate of growth – fingernails, at least 4 months; toenails, at least 6 months.

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 since in some forms of athlete's foot, yeasts and bacteria may be involved. Griseofulvin will not eradicate the bacterial or monilial infection.

Adults: A daily dose of 500 mg. will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis.

For those fungus infections more difficult to eradicate such as tinea pedis and tinea unguium, a daily dose of 1.0 gram is recommended.

Children: Approximately 5 mg. per pound of body weight per day is an effective dose for most children. On this basis the following dosage schedule for children is suggested:

Children weighing 30 to 50 pounds – 125 mg. to 250 mg. daily.

Children weighing over 50 pounds – 250 mg. to 500 mg. daily.

How Supplied

GRIFULVIN V (griseofulvin microsize) 250 mg.

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How Supplied

GRIFULVIN V (griseofulvin microsize) 250 mg. Tablets in bottles of 100 (NDC 0062-0211-60) (white, scored, imprinted "ORTHO 211").

GRIFULVIN V (griseofulvin microsize) 500 mg. Tablets in bottles of 100 (NDC 0062-0214-60) and 500 (NDC 0062-0214-70) (white, scored, imprinted "ORTHO 214").

Dispense GRIFULVIN V tablets in well-closed container as defined in the official compendia.

GRIFULVIN V (griseofulvin microsize) Suspension 125 mg. per 5 cc. in bottles of 4 fl. oz. (NDC 0062-0206-04).

Dispense GRIFULVIN V suspension in tight, light-resistant container as defined in the official compendia.

STORE AT ROOM TEMPERATURE

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869
a Johnson & Johnson Company

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