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ORTHO

ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869

OK to sign
RJ 11/23/84

NOV 8 1984

For use of Food and Drug

Antibiotic Drug Review Branch (HFN-535)
Attention: Mr. Ronald E. Joyce
Division of Generic Drugs
Center for Drugs & Biologics
5600 Fishers Lane
Rockville, MD 20857

Approved November 26, 1984
John D. Harman
Acting Commissioner of Food

NDA 62-279/S-003
NDA 62-483/S-002

Gentlemen:

Reference is made to the subject supplemental applications for our GRIFULVIN V (griseofulvin microsize) Tablets and Suspension, respectively, dated July 30, 1984. The supplements provide for revision of the products' labeling to add, under "Drug Interactions", the statement that the concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives.

Your letter of October 10, 1984, indicated that this change is acceptable but that a statement concerning "intermenstrual bleeding" or "breakthrough bleeding" should be added.

Accordingly, we have now revised our originally-proposed statement to also comply with your request. Our proposed drug interaction statement, as amended, will be as follows:

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

We intend to implement this revision to our labeling immediately.

Very truly yours,

ORTHO PHARMACEUTICAL CORPORATION

A. J. Vazakas

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

AJV/lm

017995

RECEIVED NOV 14 1984

Our reference: 62-279/S-003
62-483/S-002

Ortho Pharmaceutical Corporation
Attn: A. J. Vazakas, Ph.D.
Raritan, New Jersey 08869

October 10, 1984

Gentlemen:

This is in reference to your supplements dated July 30, 1984, proposing to revise the package insert for Grifulvin V Tablets and Suspension.

Our Division of Anti-Infective Drug Products has reviewed your proposed changes and have the following comments:

1. The change is acceptable.

2. A statement concerning "intermenstrual bleeding" or "breakthrough bleeding" should be added.

Your response is requested.

Sincerely yours,

Ronald E. Joyce
Antibiotic Drug Review Branch (HFN-235)
Division of Generic Drugs

[redacted]
HFN-235/OD
R/D REJoyce
HFN-230 (Dr. Seife)

S4002 S

Date Approved February 7, 1985

Signed [signature]

For the Commissioner of Food & Drugs

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES JAN 30 1985

OK to sign mt
JMS 2/7/85

ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869

Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
Center for Drugs & Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA 62-279/S-003
NDA 62-483/S-002

Gentlemen:

Reference is made to the subject supplemental applications for our GRIFULVIN V* (griseofulvin microsize) Tablets and Suspension, respectively, dated July 30, 1984. The supplements provide for revision of the products' labeling by addition of a statement, under "Drug Interactions", regarding the possible interaction with oral contraceptives.

The full text of our inserted statement was included in our communication of November 8, 1984. For ease of review, a copy of that letter is attached herewith.

The supplements were approved on November 26, 1984.

Accordingly, submitted herewith for each of the subject NDAs are twelve copies of the revised insert in final printed form and distributed among the copies of each application in accord with 21 CFR 314.1(e)(vi).

Very truly yours,

ORTHO PHARMACEUTICAL CORPORATION

[signature]

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

AJV/lm
attachments
*Trademark

RECEIVED
FEB 4 1985

A18691

631-10-560-3

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

Description

Griseofulvin microsize is an antibiotic derived from a species of *Penicillium*.

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
- 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

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Trichophyton tonsurans
Trichophyton mentagrophytes
Trichophyton interdigitalis
Trichophyton verrucosum
Trichophyton sulphureum
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Epidermophyton floccosum
Trichophyton megnini
Trichophyton gallinae
Trichophyton crateriform

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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.

Warnings

Usage in Pregnancy: Safe use of GRIFULVIN V (griseofulvin microsize) in pregnancy has not been established.

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. 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,

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

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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

ORTHO

631-10-560-3 Revised November 1984