62483/513

AADA 62-279/S-016 (Tablets)
AADA 62-483/S-013 (Suspension)

Johnson & Johnson Consumer Products, Inc.
Attention: Lewis Gryziewicz
199 Grandview Road
Skillman, NJ 08858

AUG 13 1997

Dear Sir:

Reference is made to your supplemental antibiotic drug applications dated January 16, 1997, submitted pursuant to 21 CFR 314.70(c)(Special Supplement-Changes Being Effected) regarding your abbreviated antibiotic applications for Grifulvin V® (Griseofulvin Tablets) microsized 250 mg and 500 mg and Grifulvin V® (Griseofulvin Oral Suspension) microsized Oral Suspension 125 mg/5 mL.

Reference is also made to your amendments dated March 18, 1997 (AADA 62-279) and July 15, 1997 (AADA 62-483).

The supplemental applications provide for revised insert labeling to include the following:

1. "Erythema multiforme-like reaction" in the ADVERSE REACTIONS section.

2. Proposed text relating to the ability of griseofulvin to induce aneuploidy in animal models in the WARNINGS section.

We have reviewed the materials submitted and have the following comment:

The proposed insert labeling and supporting data have been forwarded to the Division of Dermatologic and Dental Drug Products (HFD-540), for their review and comment. We will not take further action on these supplement until we receive their response. We will inform you of their comments when they are available.

In addition, we note you have not submitted a properly signed and executed application form with your submission.

The materials submitted are being retained in our files.

Sincerely yours,

/S/ for 8-6-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 62-279/S-016
62-483/S-013
Dup/Division File
HFD-610/Jerry Phillips
HFD-600/RF

letter out - Multiple Supplements

7/28/97

NDA NO. ______ REF. NO. [illegible]
Label Rev
SL013A1

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

JAN 16 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

AADA 62-279
GRIFULVIN V® (griseofulvin tablets) microsize Tablets

Cross-refer to:
AADA 62-483
GRIFULVIN V® (griseofulvin oral suspension) microsize Suspension 125mg/5ml

Dear Sir/Madam:

Changes Being Effected

Reference is made to our approved Abbreviated Antibiotic Drug Applications 62-279, GRIFULVIN V (griseofulvin tablets) microsize Tablets and 62-483 GRIFULVIN V (griseofulvin oral suspension) microsize Suspension 125mg/5ml. Reference is also made to a December 18, 1995 letter from the Division of Dermatologic and Ophthalmologic Drug Products, copy attached, requesting that we add "erythema multiforme" to the Adverse Reactions section of our labeling and to a May 23, 1996 telephone conversation between Frank Cross of the Division of Dermatologic and Ophthalmologic Drug Products and myself during which Mr. Cross requested that we phrase the adverse reaction as "erythema multiforme-like reaction".

In accordance with 21 CFR 314.70(c)(2)(i) at this time we wish to submit as Changes Being Effected a labeling supplement to add "erythema multiforme-like reaction" to the Adverse Reactions section of the labeling.

Additionally, we have become aware of information in the literature relating to the ability of griseofulvin to induce aneuploidy in animal models. The following articles are appended as supporting data for the addition of this warning:

1. Tiveron et al. Griseofulvin induced aneuploidy and meiotic delay in female mouse germ cells. I. Cytogenic analysis of metaphase II oocytes. Mutation Research. 1992, 266; 143-150.

2. Mailhes et al. Griseofulvin-induced aneuploidy and meiotic delay in mouse oocytes: effect of dose and harvest time. Mutation Research 1993; 300: 155-163.

3. Marchetti et al. Variation of mouse oocyte sensitivity to griseofulvin-induced aneuploidy and meiotic delay during the first meiotic division. Environmental and Molecular Mutagenesis. 1994; 23: 179-185.

JAN 17 1997
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JAN 16 1997

In accordance with 21 CFR 314.70(c)(2)(i), we wish to revise the following paragraphs to the Warnings section of the labeling from:

To read:

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 in the United States and Great Britain were inconclusive in this regard. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Because the potential for adverse effects on the human fetus cannot be ruled out, additional contraceptive precautions should be taken during treatment with griseofulvin and for a month after termination of treatment. GRIFULVIN V should not be prescribed to women intending to become pregnant within one month following cessation of therapy.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this. Griseofulvin interferes with chromosomal distribution during cell division, causing aneuploidy in plant and mammalian cells. These effects have been demonstrated *in vitro* at concentrations that may be achieved in the serum with the recommended therapeutic dosage.

Since griseofulvin has demonstrated harmful effects *in vitro* on the genotype in bacteria, plants, and fungi, males should wait at least six months after completing griseofulvin therapy before fathering a child.

Note that use during pregnancy is currently a contraindication in the GRIFULVIN V labeling.

Attached is a copy of the revised label text and the three reference articles. Added text is indicated by highlighting and deleted text is indicated by strikeout. Should you have any questions please contact me at (908) 874-1296 or Paul F. Manley at (908) 874-1239.

Sincerely,

Lewis Gryziewicz
Manager
Regulatory Affairs

att
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Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

Sent on consult

JUL 15 1997

NDA SUPPLEMENT
SL013 AL

✓AADA 62-483
GRIFULVIN V® (griseofulvin oral suspension) microsize Suspension 125mg/5ml

Cross-refer to:
AADA 62-279
GRIFULVIN V® (griseofulvin tablets) microsize Tablets

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Sir/Madam:

Changes Being Effected

Reference is made to our approved Abbreviated Antibiotic Drug Applications 62-279, GRIFULVIN V (griseofulvin tablets) microsize Tablets and 62-483 GRIFULVIN V (griseofulvin oral suspension) microsize Suspension 125mg/5ml. Reference is also made to our January 16, 1997 labeling supplement submitted as changes being effected and to our March 16, 1997 submisson of final printed labeling for the GRIFULVIN V Tablets product.

At this time please find attached twelve copies of the final printed labeling of the physician insert for GRIFULVIN V Suspension. The label text is identical to that submitted January 16, 1997 and March 16, 1997. This label was not available for the March 16, 1997 submission. We will implement this label immediately.

Should you have any questions, please call me at (908) 874-1296.

Sincerely,

Lewis Gryziewicz

Lewis Gryziewicz
Manager
Regulatory Affairs

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RECEIVED
JUL 17 1997
GENERIC DRUGS