DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-475/S-046

Pedinol Pharmacal, Inc.
Attention: Harry Gordon, Ph.D.
Regulatory Consultant
30 Banfi Plaza North
Farmingdale, NY 11735

Dear Dr. Gordon:

Please refer to your supplemental new drug application dated August 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gris-PEG® (griseofulvin ultramicrosize) Tablets, 125 mg and 250 mg.

This special supplemental new drug application changes being effected provides for the addition of "erythema multiforme – like drug reactions" to the ADVERSE REACTIONS section.

We completed our review of this supplemental new drug application, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on August 13, 1996. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

In the DESCRIPTION section, please harmonize the listings in both dosage form descriptions, using "povidone" as the appropriate USAN name for polyvinylpyrrolidone at the next printing of the package insert and report the change in the Annual Report.

If a letter communicating important information about this drug product (i.e. a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be necessary.

If you have any questions, call Frank Cross, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}
Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
nulldate

Gris-PEG®
(griseofulvin ultramicrosize)
Tablets
USP
125 mg; 250 mg

DESCRIPTION: Gris-PEG® Tablets contain ultramicrosize crystals of griseofulvin, an antibiotic derived from a species of Penicillium.

Each Gris-PEG® Tablet contains:
Active Ingredients: griseofulvin ultramicrosize... 125 mg
Inactive Ingredients: colloidal silicon dioxide; lactose; magnesium stearate; methylcellulose; methylparaben; polyethylene glycol 400 and 8000; polyvinylpyrrolidone; and titanium dioxide.

OR

Active Ingredient: griseofulvin ultramicrosize... 250 mg
Inactive Ingredients: colloidal silicon dioxide; magnesium stearate; methylcellulose; methylparaben; polyethylene glycol 400 and 8000; povidone; sodium lauryl sulfate; and titanium dioxide.

worm of the nails), when caused by one or more of the following genera of fungi: Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriform, Trichophyton sulphureum, Trichophyton schoenleini, Microsporum audouini, Microsporum canis, Microsporum gypseum and Epidermophyton floccosum. 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 agents alone. Griseofulvin is not effective in the following: bacterial infections, candidiasis (moniliasis), histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis (torulosis), tinea versicolor and nocardiosis.

CONTRAINDICATIONS: Two cases of conjoined twins have been reported since 1977 in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

This drug is contraindicated in patients with porphyria or hepatocellular failure and in individuals with a history of hypersensitivity to griseofulvin.

WARNINGS: Prophylactic Usage – Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established. Animal Toxicology - 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. Thyroid tumors, mostly adenomas but some carcinomas, have been reported in male rats receiving griseofulvin at levels of 2.0%, 1.0% and 0.2% of the diet, and in female rats receiving the two higher dose levels. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusion 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. Usage in Pregnancy – See CONTRAINDICATIONS section. Animal Reproduction Studies – It has been reported in the literature that griseofulvin was found to be embryotoxic and teratogenic on oral administration to pregnant rats. 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 hematopoietic, should be done. Since griseofulvin is derived from species of Penicillium, 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. Lupus erythematosus or lupus-like syndromes have been reported in patients receiving griseofulvin. Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may

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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. In some forms of athlete's foot, yeast and bacteria may be involved as well as fungi. Griseofulvin will not eradicate the bacterial or monilial infection.

Adults: Daily administration of 375 mg (as a single dose or in divided doses) will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis. For those fungal infections more difficult to eradicate, such as tinea pedis and tinea unguium, a divided dose of 750 mg is recommended.

Pediatric Use: Approximately 3.3 mg per pound of body weight per day of ultramicrosize griseofulvin is an effective dose for most pediatric patients. On this basis, the following dosage schedule is suggested: Children weighing 35-60 pounds – 125 mg to 187.5 mg daily. Pediatric patients weighing over 60 pounds – 187.5 mg to 375 mg daily. Children and infants 2 years of age and younger – dosage has not been established.

Clinical experience with griseofulvin in children with tinea capitis indicates that a single daily dose is effective. Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

HOW SUPPLIED: Gris-PEG® (griseofulvin ultramicrosize) Tablets, 125 mg, white, scored, elliptical-shaped, embossed "Gris-PEG®" on one side and "125" on the other. Gris-PEG® (griseofulvin ultramicrosize) Tablets, 250 mg, white, scored, capsule-shaped, embossed "Gris-PEG®" on one side and "250" on the other. The 125 mg strength is available in bottles of 100 (NDC 0023-0763-04). The 250 mg strength is available in bottles of 100 (NDC 0023-0773-04) and 500 (NDC 0023-0773-50). Both strengths are film-coated.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

STORAGE: Store Gris-PEG® tablets at controlled room temperature 15°-30°C (59°-86°F) in tight, light-resistant containers.

Manufactured for
ALLERGAN Herbert
Skin Care Division Of Allergan, Inc.
Irvine, California 92612, U.S.A.

by **SANDOZ**
PHARMACEUTICALS
CORPORATION
East Hanover, NJ 07936

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