DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA

Pedinol Pharmacal, Inc.

Dear :

To obtain needed pediatric information on griseofulvin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the studies outlined below:

Background Information:

In the United States, tinea capitis (or ringworm of the scalp) is caused most commonly by *Trichophyton tonsurans* (90% of patients in North America) and *Microsporum canis*. This infection occurs most frequently in children, ages 3 to 9 years. It is likely that tinea capitis may occur in patients less than three years of age, especially if they are in daycare or have older siblings.

Treatment of tinea capitis requires oral therapy. Currently, only griseofulvin is approved for this indication and only in patients 2 years of age and older. Griseofulvin is available as a tablet in the ultramicrosize form, which is more bioavailable than the microsize form (available in a tablet and suspension). The ultramicrosize griseofulvin has lower dosing recommendations in the labeling when compared to the microsized. The suspension is only available for griseofulvin microsize. The labeling for the microsize formulation of griseofulvin recommends a maximum daily dose of 250 mg in children weighing 30 to 50 pounds (13.6 kg to 22.7 kg) which equates to a maximum dose of 11 to 18.3 mg/kg/day in this body weight range. However, these maximum labeled daily doses are lower than the dose currently recommended in the Red Book[1], which is 25 mg/kg/day. In addition, the recommended duration of therapy is 6-8 weeks, although the labeling recommends use only up to 6 weeks. Dosing recommendations have not been established for children < 2 years of age.

Several griseofulvin products are approved and marketed, including two oral suspension formulations and three tablet formulations. Griseofulvin tablets are available in both microcrystalline (microsize) and ultramicrocrystalline (ultramicrosize) formulations. The oral suspension is only available as microcrystalline griseofulvin. Additional tablets have been marketed but are now discontinued. Currently available products include:

- Griseofulvin, microcrystalline, 125mg/5 cc oral suspension

[1] *2003 Red Book: Report of the Committee on Infectious Diseases,* 26th edition. American Academy of Pediatrics, 2003.

- Gris-PEG®, ultramicrocrystalline, 125, 250 mg tablet
- Grifulvin V®, microcrystalline, 125, 250, 500 mg tablet
- Grifulvin V®, microcrystalline, 125mg/5 cc oral suspension
- Fulvicin U/F®, microcrystalline, 250, 500 mg tablet

In response to a previous written request, there has been one well-controlled clinical study in pediatric patients examining the efficacy of fluconazole (Diflucan®) for the treatment of dermatophyte infections. Fluconazole treatment at 6 mg/kg was not superior to the labeled griseofulvin dose of 11mg/kg for 4-6 weeks. See Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies at

http://www.fda.gov/cder/pediatric/Summaryreview.htm

Although doses of 20-25 mg/kg/day of griseofulvin are recommended, according to the literature, only one double blind, randomized trial has evaluated this higher dose in children with tinea capitis. In this trial, the cure rate for 20 mg/kg in 25 children was 84 % and superior to terbinafine. Standard doses of griseofulvin have been superior or similar to other antifungal agents (itraconazole, ketoconazole or terbinafine), especially with regard to *Microsporum canis*. However, other trials have suggested that standard doses of griseofulvin treatment are inferior to these therapies.

Nonclinical Supporting Study to be Performed:

Prior to studying griseofulvin in pediatric patients, an *in vitro* drug interaction study must be performed.

Objectives:
To determine drug metabolism pathways in order to identify potentially important drug-drug interactions

To explore whether griseofulvin is an inhibitor or inducer of metabolic enzymes in order to assess its potential to alter the metabolism of other drugs

Study Design:
Please refer to "Guidance for Industry, Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies *In Vitro*" at

http://www.fda.gov/cder/guidance/clin3.pdf

The study should be adequate to characterize the isoenzymes responsible for the metabolism of griseofulvin.

Study Endpoints:
Explore and identify the principal metabolizing routes of griseofulvin, isoenzymes responsible for the metabolism (or inhibition of metabolism) of griseofulvin and potential drug interactions.

Study Evaluation:
The study should ascertain isoenzymes responsible for metabolism of griseofulvin and should also ascertain which isoenzymes could inhibit the metabolism of griseofulvin. Describe metabolic pathways and potential drug-drug interactions.

The results of the *in vitro* study, as well as information available in the literature should be used to identify the moieties to be measured in the human pharmacokinetic studies. Prior to the initiation of studies in pediatric patients the sponsor is encouraged to discuss their *in vitro* findings with the Agency.

Type of Studies to be Performed:
Study 1: Pharmacokinetics and safety of griseofulvin in pediatric patients with tinea capitis. An alternative to Study 1 is to incorporate plasma sampling for the measurement of griseofulvin and its metabolite(s) into Study 2 using population pharmacokinetics for analysis. Please refer to "Guidance for Industry, Population Pharmacokinetics" at

http://www.fda.gov/cder/guidance/1852fnl.pdf

Study 2: Clinical safety and efficacy study in pediatric patients with tinea capitis.

Indication to be Studied: Treatment of tinea capitis in pediatric patients

Objectives:
Study 1:

To compare the pharmacokinetics at steady-state at the maximum labeled daily dose of the microsized formulation of griseofulvin in patients with body weight $\leq$ 22 kg and the maximum Red Book recommended dose (See dosing regimens in Study Design under Study 1.)

Study 2:

To compare the clinical safety and efficacy of griseofulvin at the maximum labeled daily dose of the microsized formulation of griseofulvin in patients with body weight $\leq$ 22 kg and the maximum Red Book recommended dose in children with tinea capitis

Study Design:
Study 1: The pharmacokinetic study should be an open-label, multiple dose study in pediatric patients $\leq$ 22 kg with tinea capitis. Microsize griseofulvin will be administered with food or whole milk, depending on the age of the patient.

Study 1 and 2 dosing regimens are as follows:

- Maximum labeled dose (10 mg/kg for patients $\leq$ 13.6 kg or 250 mg for patients > 13.6 kg) for 8 weeks
- Maximum Red Book-recommended dose (25 mg/kg/day) for 8 weeks

Plasma sampling for the determination of griseofulvin and metabolite(s) must be done prior to the attainment of steady state and over a dosing interval at steady state and to allow for the determination of half-life.

Study 2: Randomized, investigator-blinded, safety and efficacy trial comparing the maximum labeled dose to the maximum Red Book recommended dose of griseofulvin (see Study 1, dosing regimens). Patients with tinea capitis will be randomized 1:2 (maximum labeled dose vs. maximum Red Book-recommended dose, respectively). Efficacy (i.e., fungal culture and potassium hydroxide wet mount) and safety measures will be collected at baseline and every 2 weeks on treatment, including end-of-treatment (study weeks 2, 4, 6, 8 and 12). No antifungal shampoos will be allowed during the study period.

Should a population pharmacokinetic approach be used, an a priori plasma sampling plan must be in place to ensure that adequate data are obtained to allow for a proper population analysis.

Special considerations for Studies 1 and 2: A Data Monitoring Committee with pertinent expertise must be used to provide ongoing oversight of patient safety. The operating plan for the DMC should be submitted to the division for review and comment.

Inclusion/Exclusion Criteria:
Studies 1 and 2:
Inclusion criteria:

- Patients with a diagnosis of tinea capitis, based on clinical exam and positive microscopic evaluation (e.g., potassium hydroxide wet mount). The patients enrolled in these studies should be representative of the patients who will be treated in the U.S., with regard to both demographics and etiologic organism. All patients must have appropriate fungal studies (including microscopic evaluation and culture). Patients with positive fungal culture should be included in the modified intent to treat (mITT) population. Those patients with positive microscopic exam but whose culture is negative should be included in the safety evaluation.
- Patients should have normal baseline laboratory parameters (e.g., liver function tests, CBC and differential, renal function).

Exclusion criteria:

- Patients with known anaphylaxis to penicillin or significant renal or hepatic dysfunction.
- Patients on concomitant medical therapies, including those identified during the nonclinical study known to interfere with griseofulvin metabolism.

Study Population and Age Groups to be Studied:
Pediatric patients ages 6 months-10 years, with weight $\leq$ 22 kg. Inclusion of patients must reflect the epidemiology of tinea capitis, with enrichment (see numbers of patients to be studied) of patients between 6-36 months of age.

Number of Patients to be Studied or Power of Study to be Achieved:
Study 1: Patients $\leq$ 22 kg: 20 evaluable patients for pharmacokinetic assessment in each of the two planned dosing regimens. Approximately one-half of the patients should weigh less than 15 kg (the average body weight of a 3 year old patient). The number of patients should be approximately evenly distributed within the age range.

The total volume of blood to be drawn (not to exceed acceptable limits) and the pharmacokinetic methods to be employed in the data analysis must be determined a priori and stated in the protocol.

If population pharmacokinetics with sparse sampling is used in Study 2 (in lieu of Study 1) blood samples must be dispersed throughout the dosing interval to ensure proper parameter estimation. Please refer to Draft Guidance for Industry, "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products."

Study 2: The larger N of the following should be used:

The study must be sized to detect adverse events with a probability of 95 % that occur at an incidence of 1% with the maximum Red Book-recommended dose of griseofulvin microsize. Therefore, Study 2 must have at least 300 patients who complete the course of maximum Red Book dose treatment arm, with a minimum of 80 patients evaluable for safety between 6-36 months of age. Similarly, a minimum of 150 patients must complete the highest labeled dose treatment arm with a minimum of 40 patients evaluable for safety between 6-36 months of age. (See dosing regimens in Study Design under Study 1.)

Dose	Total	Children 6 - 36 months
Maximum Red Book-recommended Daily Dose	300	80
Maximum Labeled Daily Dose	150	40

In addition, the study must be powered to show superiority in the mITT population of maximum Red Book-recommended dose to the maximum labeled dose of griseofulvin with a test of hypothesis using an alpha of 0.05 (which may require more than a total of 450 patients.)

Study Endpoints:

Study 1: Study design including sample collection must ensure sufficiently accurate estimates of pharmacokinetic parameters in pediatric patients at steady-state. The parameters to be obtained should be based on the pharmacokinetic approach used (e.g., AUC, Cmax, Tmax, $T_{1/2}$, Cmin, and Cl/F).

Study 2: Percentages of patients with complete cure (mycologic and clinical) at 8 weeks in the mITT population (those patients who are randomized and dispensed medication and had a positive culture for a relevant organism at baseline). A subgroup analysis for each of the dermatophyte species determined by fungal culture is needed. In addition, a subgroup analysis of clinical failures to determine resistance patterns (MIC, etc.) must be performed. Subgroup analysis by age, race and sex must also be performed. All patients who have received at least one dose of griseofulvin will be included in the safety analysis.

Study Evaluation:

Study 1: The pharmacokinetics must be compared between the two dosing regimens. The effects of age on the pharmacokinetics will be evaluated.

Study 2: Efficacy (i.e., fungal culture and potassium hydroxide wet mount) and safety assessments must be performed at baseline and every 2 weeks on treatment, to include an end-of-treatment evaluation and evaluation at 4 weeks post therapy (study weeks 2, 4, 6, 8 and 12). Safety monitoring must include monitoring for adverse events as well as monitoring of liver and renal function and CBC with differential. Patients should be followed until resolution (or stabilization) of adverse events or abnormal laboratory parameters. All patients who have received at least one dose of griseofulvin will be included in the safety analysis.

Statistical Information:

Study 1: Descriptive statistics (mean, median, range, standard of deviation, coefficient of variation, etc) for the pharmacokinetic parameters as outlined under study endpoints.

Study 2: The superiority hypothesis tests will be tested. The primary efficacy variable (complete cure) will be analyzed using an appropriate statistical method for the study design, stratified by center. All efficacy analysis will be presented for the ITT and mITT populations. The ITT population is defined as those patients randomized in the study and dispensed treatment. The mITT population is defined as those patients randomized in the study and dispensed treatment who have positive fungal culture. Safety analysis will be presented for all patients who have received at least one dose of griseofulvin.

Drug Information:

Route of administration: Oral
Dosage form: Microsize suspension of griseofulvin
Dosing Regimen: Once daily for eight weeks of maximum labeled dose (10 mg/kg for patients $\leq$ 13.6 kg or 250 mg for patients > 13.6 kg) or maximum Red Book dose (25 mg/kg/day)

Drug Specific Safety Concerns and Drug Interactions:

Griseofulvin has been associated with hepatic injury (including failure), proteinuria, hematologic anomalies (leukopenia, granulocytopenia and neutropenia) and peripheral neuropathy. In addition, skin rashes are common. Gastrointestinal complaints, headaches and confusion are also common. Serious hypersensitivity reactions (including cross-sensitivity with penicillin and erythema multiforme-like drug reactions), photosensitivity reactions, lupus and lupus-like syndromes have been reported. Drug interactions with salicylates, warfarin-type anticoagulants, oral contraceptives, and barbiturates may occur, necessitating dosing adjustments.

All patients who have received at least one dose of griseofulvin will be included in the safety analysis.

Additional Information Required:

Summary of the susceptibility patterns of the organisms and response to therapy must be provided.

Labeling that May Result From the Studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of Reports to be Submitted:
Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for Submitting Reports of the Studies:
Reports of the above studies must be submitted to the Agency on or before August 31, 2008. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:
As per the Best Pharmaceuticals for Children Act, section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - COMPLETE RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, please call , Senior Regulatory Management Officer, at .

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Deputy Director
Office of Drug Evaluation III
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/

Julie Beitz
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