

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 62-178

Name: Grisactin® Ultra
(Griseofulvin Ultramicrosize Tablets)

Sponsor: Ayerst Laboratories

Approval Date: March 13, 1980

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-178

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-178

APPROVAL LETTER



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

Wfd-535

Our reference:
62-178

MAR 13 1980

Ayerst Laboratories
Attention: Henry S. Perdue, Ph.D.
685 Third Avenue
New York, New York 10017

Gentlemen:

We have completed our review of your Form 6 application dated August 30, 1979, amended March 10, 1980, which provides for the manufacture of griseofulvin (ultramicrosize) tablets at your facilities in Rouses Point, New York. The application is considered to be satisfactory. An approved copy is enclosed for your file.

Your firm is now authorized to request release of batches of griseofulvin (ultramicrosize) 125 mg. and 250 mg. tablets, manufactured, controlled, packaged and labeled as described in the application. We have requested that monograph 449.120d be revised to provide for the certification of your tablets.

The application as approved provides for a maximum batch size of (b) (4) - 125 mg. or 250 mg. tablets. An expiration date of 24 months should be used on each batch of the drug submitted for release.

Please be advised that the labeling for this drug is under review. Labeling revisions and/or additional bioavailability studies may be required in the near future. The currently approved package insert for this drug states that the gastrointestinal absorption of ultramicrosize griseofulvin tablets is approximately twice that of conventional microsize griseofulvin tablets. In recent months bioavailability studies have come to the attention of FDA which indicate that such a statement regarding dose proportion may not be valid.

Samples from the first three released batches should be set aside for stability studies. The data should be submitted at 6 month intervals the first year and annually thereafter.

The Form 6 application should be kept up to date. Any changes or revisions in the manufacturing process, controls, laboratory procedures or personnel should be submitted as an amendment to the application.

Sincerely yours,

Marvin Seife 3/13/80

Marvin Seife, M.D.
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs

Enclosure

cc:

NYK-DO

HFD-535

HFD-535/OD

HFD-430/lab.

HFD-332/FGeissel

HFD-332/KWhitley

HFD-535/MEisler

HFD-610

HFD-500/DHare

HFD-530/Dr.Seife

HFD-535/JDHarrison *JDH 3/12/80*

Prepared by: WEMagner

typ. 3/12/80 hb

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ANTIBIOTIC APPLICATION

Form approved;
OMB No. 57-R0126

IMPORTANT: No batches of Antibiotic Drugs may be certified or released unless this form, Antibiotic Application, Form FD 1675, has been filed with the Food and Drug Administration (21 CFR, Parts 430 through 460).

APPLICABLE PROCEDURES	Check one	FOOD AND DRUG ADMINISTRATION USE ONLY	
Form 5 request under 431.17 to provide for certification of a new antibiotic or antibiotic-containing product.		DATE APPROVED 3/13/80	ACCOUNT NO.
Form 6 data to accompany or precede every initial request under 431.1 for certification of an antibiotic drug covered by existing Regulations, Section _____	X	SIGNED <i>Maurice Seife, M.D.</i> (For the Commissioner of Food and Drugs) Food and Drug Administration Department of Health, Education, and Welfare	
Form 5 amendment, Regulation Section _____, if known.			
Form 6, Regulation Section <u>431.17</u>			
NAME OF APPLICANT (Last, First, MI) AYERST LABORATORIES			DATE OF APPLICATION
ADDRESS (Number, Street, City, State, ZIP Code) 685 THIRD AVENUE, NEW YORK, NEW YORK 10017			
NAME OF DRUG GRISACTIN ULTRA (griseofulvin ultramicrosize)			

Commissioner
Food and Drug Administration
Department of Health, Education, and Welfare
Rockville, Maryland 20852

Attention: Certifiable Drug Review, Staff (HFD-535)

In accordance with regulations promulgated under Section 507 of the Federal Food, Drug, and Cosmetic Act, as amended, we hereby submit this application with respect to an antibiotic product.

Attached hereto, in triplicate (except for the information required under item 9 (a) through (f) which is submitted in single copy) and constituting a part of this application are the following:

1. A full list of the articles used as components of the drug. This list should include all substances used in the fermentation, synthesis, extraction, purification or other method of preparation of any antibiotic and in the preparation of the finished dosage form, regardless of whether they undergo any change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

2. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per millimeter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

3. A complete description of the methods and processes used in manufacturing, packing and labeling of the drug to preserve its identity, strength, quality, and purity in conformity with good manufacturing practices including:

- (a) Name and location of each plant conducting the operations.
- (b) Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.
- (c) Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material used in the fermentation, synthesis, extraction, and purification of the drug and for each ingredient used in the manufacture of the drug that is to be dispensed.
- (d) If it is a drug produced by fermentation:
 - (i) Source and type of microorganism used to produce the drug.
 - (ii) Composition of media used to produce the drug.
 - (iii) Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.
 - (iv) Name and composition of preservative, if any, used in the broth.
 - (v) A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, demulsifiers, and all other agents used.
 - (vi) If the drug is produced by a catalytic hydrogenation process, (such as tetracycline from chlortetracycline), a complete description of the process, including the name of the catalyst used, how it is removed, and how the drug is extracted and purified.

- (e) If it is a drug that is synthesized by chemical processes, a detailed description of each chemical reaction with graphic formulas used to produce the drug, including the names and amounts of all substances used in the process.

(NOTE: If the applicant is not the manufacturer of the antibiotic used in making the drug, in lieu of the information required in 3(a) through 3(e), he should include the name and address of the manufacturer.)

- (f) Method of preparation of the master formula records and individual batch records and manner in which these records are used.
- (g) Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.
- (h) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up the batch according to the formula card, and at what stage and by whom this is done.
- (i) At what point in the process the drug is mixed homogeneously and a description of the equipment used for this purpose and its total capacity in terms of pounds, kilograms, gallons, or liters of the drug and the maximum quantity of the drug that is mixed in such equipment.
- (j) A description, where applicable, of all equipment used in the fermentation, synthesis, extraction, purification, filtration, sterilizing, grinding, blending, mixing, tableting, encapsulating, filling, packaging, and labeling of the drug.
- (k) If it is a sterile drug, a description of the methods used to insure the sterility of each batch and the controls used for maintaining its sterility, including a detailed description of the sterile areas where the drug is produced and packaged.
- (l) Additional procedures employed which are designed to exclude contaminants (e.g., other drug substances, extraneous materials, etc.) and otherwise assure proper control of the product.
- (m) Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug container to insure their suitability for the intended use.
- (n) Controls used in the packaging and labeling of each batch to insure the standards of identity, strength, quality and purity of the drug.
- (o) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.
- (p) Precautions to insure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling, storage, and inventory control.
- (q) Copies of all printed forms used by the applicant in the manufacture, packaging, and labeling of a batch.
- (r) The name of each person responsible for each of the above operations and information concerning his scientific training and experience.

4. A complete description of the tests and methods of assay and other controls used during the manufacture of the batch and after it is packaged.

- (a) Details of analytical procedures for all active ingredients. The analytical procedures should be capable of determining the active components and of assuring the identity of such components.
- (b) Standards used for acceptance of each lot of the finished drug.
- (c) A detailed description of the collection of the samples to be tested by the applicant and by the Food and Drug Administration.

- (d) Copies of all printed forms used by the applicant in the laboratory control of raw ingredients and the finished batch.

- (e) A complete description of the laboratory facilities used in such controls, including:

- (i) The location of the laboratory in relation to the plant where the drug is manufactured,
- (ii) A description of the laboratory equipment available for performing tests and assays, and
- (iii) The names of the persons who will be responsible for conducting the required laboratory tests and information concerning their scientific training and experience.
- (f) If the applicant uses the services of a consulting laboratory, the name and address of such laboratory and a statement from such laboratory that includes the information required under 4(a), (b), and (e).
- (g) An explanation of the exact significance of any batch numbers used in the manufacturing, processing, packaging, and labeling of the drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.
- (h) A complete description of, and data derived from, stability studies of the potency and physical characteristics of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new antibiotic, for the finished dosage form of the drug, the container including a multiple-dose container in which it will be marketed, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed.
- (i) The expiration date needed to preserve the identity, strength, quality, and purity of the drug until it is used.

5. The following samples shall be submitted with the application or as soon thereafter as they become available:

- (a) If it is a new antibiotic: 10 grams of the applicant's reference standard if an official standard has not been designated, plus 5 grams from each of three separate batches. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.
- (b) If it is a dosage form: 6 immediate containers (or 30 tablets or capsules) from each of three separate batches, except that if it is a sterile drug 30 containers shall be submitted from each of three batches.
- (c) Include for samples submitted pursuant to items 5(a) or 5(b), detailed results of all laboratory tests made to determine the identity, strength, quality and purity of the batch represented by the sample.

- (d) Additional samples shall be submitted on request.

- (e) The requirements of items 5(a) or 5(b) may be waived in whole or in part on request of the applicant, or otherwise, when such samples are not necessary.

6. Each copy of the application shall contain a copy of each label and all other labeling to be used for the drug.

- (a) Each label, or other labeling, should be clearly identified or show its position on, or the manner in which it accompanies, the market package.

(b) The labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use, or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to laymen.

(c) If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purpose for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with 201.100 or 201.105.

(d) If no established name exists for a new antibiotic, the application shall propose a nonproprietary name for use as the established name for the substance.

(e) Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not be approved prior to the submission of the final printed label and labeling of the drug. No application may be approved if the labeling is false or misleading in any particular. *(If the article is a prescription drug, copies of proposed advertising may be submitted optionally for comment or approval).*

7. State whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

8. It is understood that the labeling, and advertising for the antibiotic drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will also contain substantially the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions, contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until an amendment providing for a change is approved by the Food and Drug Administration.

9. Full reports of investigations that have been made to show whether or not the drug is safe for use and efficacious in use.

If this is a Form 5 application submit one copy of (a) through (f) below

(a) An application may be found unsatisfactory unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the proposed labeling and includes all the following:

(i) Detailed reports of the preclinical investigations, including studies made on laboratory animals, in which the methods used and the results obtained are clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or premenopausal women.

(ii) Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations

made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

(iii) All information pertinent to an evaluation of the safety and efficacy of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application or pertinent information about any relevantly related drug. An adequate summary may be acceptable in lieu of a reprint of a published article which only supports other data submitted. Include any evaluation of the safety or efficacy of the drug that has been made by the applicant's medical department, expert committee, or consultants.

(iv) If the drug is a combination of previously investigated or marketed drugs an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

(b) An application may be found unsatisfactory unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the efficacy of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(c) The complete composition and/or method of manufacture of the drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in item 1, 2, 3 or 4 of the application in any way that would bias an evaluation of the report.

(d) An application shall include a complete list of the names and post office addresses of all investigators who received the drug.

(e) The information required by 9(a) through 9(d) may be incorporated in whole or in part by specific reference to information submitted under the provision of § 312.1.

(f) Explain any omission of reports from any investigator to whom the investigational drug has been made available. The unexplained omission of any reports of investigations made with the drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, that would bias an evaluation of the safety of the drug or its efficacy in use constitutes grounds for finding the application unsatisfactory.

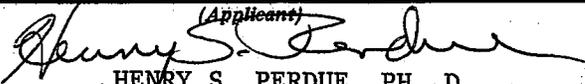
(g) If this is a Form 6 application, in lieu of the information required in 9(a) through 9(f) it should include data adequate to demonstrate that the drug is comparable to the drug for which certification has previously been provided.

10. If this is an amendment, full information on each proposed change concerning any statement made in the approved application. After an application is approved, an amendment may propose changes. An amendment should be submitted for any change beyond the variations

provided for in the approved application. An amendment may omit statements made in the approved application concerning which no change is proposed. Any mailing or promotional piece used after the drug is placed on the market is labeling requiring an amendment. An amendment should be submitted for proposed changes in labeling. If a change is made in the components, composition, manufacturing methods, facilities or controls, or in the labeling or advertising from the representations in an approved application and the drug is marketed before an amendment is approved for such change, certification of the drug may be suspended.

Very truly yours,

AYERST LABORATORIES

(Applicant)

Per _____ HENRY S. PERDUE, PH. D.

VICE PRESIDENT, REGULATORY AFFAIRS

(Indicate Authority)

This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States. The data specified under the several numbered headings should be on separate sheets or sets of sheets, suitably identified. The sample of the drug, if sent under

separate cover, should be addressed to the attention of the National Center for Antibiotic Analysis and identified on the outside of the shipping package with the name of the applicant and the name of the drug as shown on the application. All applications and correspondence should be submitted in triplicate except the information required under item 9(a) through (f) which should be submitted as a single copy attached to the original copy of the application.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-178

LABELING

GRISACTIN[®]
Ultra
 (griseofulvin
 ultramicrosize)

Ayerst[®]

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Griseofulvin is an oral fungistatic antibiotic for the treatment of superficial mycoses. It is derived from a species of *Penicillium*.

GRISACTIN Ultra tablets contain 125 mg griseofulvin ultramicrosize and 250 mg griseofulvin ultramicrosize.

ACTION

Griseofulvin is fungistatic with *in vitro* activity against various species of *Microsporum*, *Epidermophyton*, and *Trichophyton*. It has no effect on bacteria or on other genera of fungi.

Griseofulvin is deposited in the keratin precursor cells and has a greater affinity for diseased tissue. The drug is tightly bound to the new keratin which becomes highly resistant to fungal invasions.

Controlled bioavailability studies of GRISACTIN Ultra have demonstrated comparable values to blood levels regarded as adequate. The efficiency of gastrointestinal absorption of ultramicrocrystalline griseofulvin is approximately twice that of the conventional microsize griseofulvin. This factor permits the oral intake of half as much griseofulvin per tablet but there is no evidence, at this time, that this confers any significant clinical differences in regard to safety and efficacy.

INDICATIONS

Griseofulvin is indicated for the treatment of ringworm infections of the skin, hair, and nails, namely:

Tinea corporis
Tinea pedis
Tinea cruris
Tinea barbae
Tinea capitis

Tinea unguium (onychomycosis) 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 schoenleinii
Microsporum audouinii
Microsporum canis
Microsporum gypsum
Epidermophyton floccosum

NOTE: Prior to therapy, the type of fungi responsible for the infection should be identified.

The use of this 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
 Nocardiosis

CONTRAINDICATIONS

This drug is contraindicated in patients with porphyria, 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 has 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 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.

Usage in Pregnancy

The safety of this drug during pregnancy has not been established.

GRISACTIN® Ultra (griseofulvin ultramicronize) cont'd.

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. Additional animal reproduction studies are in progress.

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. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy.

Barbiturates usually depress griseofulvin activity and concomitant administration may require a dosage adjustment of the antifungal agent.

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

Adults: Daily administration of 250 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 500 mg is recommended.

Children: Approximately 2.5 mg per pound of body weight per day is an effective dose for most children. On this basis the following dosage schedule is suggested: Children weighing 30-50 pounds—62.5 mg to 125 mg daily. Children weighing over 50 pounds—125-250 mg daily. Children 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

GRISACTIN® Ultra tablets, 125 mg: white, compressed tablets impressed with the trade name and dosage strength, in bottles of 100 (NDC 0046-0434-81) and 500 (NDC 0046-0434-85).

GRISACTIN® Ultra tablets, 250 mg: white, compressed tablets impressed with the trade name and dosage strength, in bottles of 100 (NDC 0046-0435-81) and 500 (NDC 0046-0435-85).

Store at room temperature (approximately 25°C).

**AYERST LABORATORIES
INCORPORATED**
New York, N.Y. 10017

NDC 0046-0435-85 500 Tablets

Grisactin® Ultra

(griseofulvin
ultramicrosize)

250 mg

NOTE: Dispense in child resistant packaging.
This package not for household use.

CAUTION: Federal law prohibits
dispensing without prescription.

Ayerst.

AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

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ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying
Descriptive Literature.

Pat. Pending

STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C).

Printed in U.S.A.

NDC 0046-0435-85 500 Tablets

Grisactin® Ultra

(griseofulvin
ultramicrosize)

250 mg

NOTE: Dispense in child resistant packaging.
This package not for household use.

CAUTION: Federal law prohibits
dispensing without prescription.

Ayerst.

AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

137

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying
Descriptive Literature.

Pat. Pending

STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C).

Printed in U.S.A.

NDC 0046-0435-81 100 Tablets

Grisactin® Ultra

(griseofulvin
ultramicrosize)

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

Ayerst.

AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

135

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying
Descriptive Literature.

Pat. Pending

STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C).

Printed in U.S.A.

NDC 0046-0435-81 100 Tablets

Grisactin® Ultra

(griseofulvin
ultramicrosize)

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

Ayerst.

AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

135

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying
Descriptive Literature.

Pat. Pending

STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C).

Printed in U.S.A.

NDC 0046-0434-85 500 Tablets

Grisactin® Ultra

(griseofulvin ultramicrosize)

125 mg

NOTE: Dispense in child resistant packaging. This package not for household use.

CAUTION: Federal law prohibits dispensing without prescription.



AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying Descriptive Literature.
Pat. Pending
STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C.)

Printed in U.S.A.

136

NDC 0046-0434-85 500 Tablets

Grisactin® Ultra

(griseofulvin ultramicrosize)

125 mg

NOTE: Dispense in child resistant packaging. This package not for household use.

CAUTION: Federal law prohibits dispensing without prescription.



AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying Descriptive Literature.
Pat. Pending
STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C.)

Printed in U.S.A.

136

NDC 0046-0434-81 100 Tablets

Grisactin® Ultra

(griseofulvin ultramicrosize)

125 mg

CAUTION: Federal law prohibits dispensing without prescription.



AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying Descriptive Literature.
Pat. Pending
STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C.)

Printed in U.S.A.

134

NDC 0046-0434-81 100 Tablets

Grisactin® Ultra

(griseofulvin ultramicrosize)

125 mg

CAUTION: Federal law prohibits dispensing without prescription.



AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

ANTIFUNGAL-ANTIBIOTIC



Usual Dosage: Read Accompanying Descriptive Literature.
Pat. Pending
STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C.)

Printed in U.S.A.

134

0435

3 TABLETS

Grisactin[®] Ultra

(griseofulvin
ultramicrosize)

Each tablet contains **250 mg**

For full product information, see
accompanying package circular.

PHYSICIAN'S COMPLIMENTARY PACKAGE

CAUTION: Federal law prohibits dispensing
without prescription.

Ayerst

Pat. Pending

NOTE: PACKAGE NOT CHILD-RESISTANT
Printed in U.S.A.

DIRECTIONS FOR USE _____

269



STORE AT ROOM TEMPERATURE (APPROXIMATELY 25° C).

0435

3 TABLETS

Grisactin[®] Ultra

(griseofulvin
ultramicrosize)

Each tablet contains **250 mg**

For full product information, see
accompanying package circular.

PHYSICIAN'S COMPLIMENTARY PACKAGE

CAUTION: Federal law prohibits dispensing
without prescription.

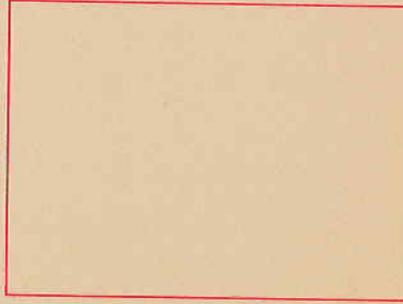
Ayerst

Pat. Pending

NOTE: PACKAGE NOT CHILD-RESISTANT
Printed in U.S.A.

DIRECTIONS FOR USE _____

269



STORE AT ROOM TEMPERATURE (APPROXIMATELY 25° C).

Grisactin® Ultra
(griseofulvin
ultramicrosize)
250 mg Tablets

Grisactin® Ultra
(griseofulvin
ultramicrosize)
250 mg Tablets

0435-53

Grisactin® Ultra

(griseofulvin
ultramicrosize)
250 mg Tablets

for treatment of
onychomycosis and
other stubborn tinea

Each tablet contains 250 mg
griseofulvin ultramicrosize.

NOTE: PACKAGE NOT CHILD-RESISTANT.

CAUTION: Federal law prohibits
dispensing without prescription.

STORE AT ROOM TEMPERATURE
(APPROXIMATELY 25° C).

Ayerst

AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

Printed in U.S.A.

833

Pat. Pending

5 CARDS

3 TABLETS EACH

Grisactin® Ultra
(griseofulvin
ultramicrosize)
250 mg Tablets

for treatment of
onychomycosis and
other stubborn tinea

For full product information,
see accompanying package circular.

Grisactin®
Ultra
(griseofulvin
ultramicrosize)
250 mg Tablet

USUAL DOSAGE
Adults—
250 mg daily
Children—
2.5 mg/lb daily

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-178

LABELING REVIEWS

INTRA-ADMINISTRATIVE REFERRAL

Jacket Identification,
Type and Number

Issuance Date 2/1/60

Overst
Griseofulvin Ultra-
microsize Tablets 62-178

To	Referrals and Recommendations
<p><i>Mr. Magner</i></p>	<p><i>Labeling review</i></p> <ol style="list-style-type: none"> <i>1. Labels - satisfactory</i> <i>2. Package insert</i> <ol style="list-style-type: none"> <i>a. The statement "The efficiency of gastrointestinal absorption of ultramicro-crystalline griseofulvin is approximately twice that of the conventional microsize griseofulvin." will have to be proven by the bioavailability studies. (Second paragraph of the "Action" section.)</i> <i>b. In the "Dosage and Administration" section "Children:" dosage, the word between "is" and "continued" should be "not" in the last sentence.</i> <p style="text-align: right;"><i>J. Powers</i> <i>2/1/60</i></p>

This form to be used in lieu of yellow Agency Route Slip when requesting comments or recommendations.

Division name only to be used in "To" column. If individual is to be designated, indicate name in body of form to right of division.

Draw double line under conclusion of individual's dated recommendation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-178

CHEMISTRY REVIEWS

CHEMISTRY REVIEW NOTES

November 26, 1979

Re: Form 6 - #62-178

Griseofulvin Ultramicrosize Tablets
125 mg/tab and 250 mg/tab
Submitted by Ayerst Laboratories

Ayerst, a new manufacturer of Griseofulvin Ultramicrosize Tablets, wishes to make a new product using different raw ingredients.

The applicable monograph, 21 CFR 449.120d, states that the tablets are composed of ultra microsize crystals of griseofulvin dispensed in polyethylene glycol 6000 and that the griseofulvin used conforms to 21 CFR 449.20(a)(1) (griseofulvin microsize). Ayerst is seeking approval of a griseofulvin ultramicrosize tablet dispensed in (b)(4) and (b)(4) griseofulvin used as the raw ingredient. The specific (b)(4) griseofulvin (b)(4) would have to be waived for (b)(4) on some other provisions made, such as, (1) proposing a new bulk monograph for griseofulvin ultramicrosize powders, (2) proposing a new monograph for this tablet, or (3) revising 449.120d to provide for this tablet.

Ayerst purchases the (b)(4) griseofulvin from (b)(4) (b)(4) which meets 21 CFR 449.20 requirements except for specific (b)(4). The (b)(4) griseofulvin (b)(4)

good test for classifying griseofulvin powder (p. 99). The other raw ingredients meet USP, NF or other compendia requirements.

The controls used during manufacture appear to be adequate.

The standards for acceptance of the finished product are slightly different from 449.120d. The company performs an identity test (UV) and dissolution test on the product and does not propose to do the solubility characteristic test, which is a monograph requirement. As part of our testing of this product, we did the dissolution test submitted by the company. It employs the paddle method using sodium lauryl sulfate as the dissolution medium and (b)(4) in the analytical procedure. We found the dissolution medium to be satisfactory but using (b)(4) for the analysis would present problems, if the method were used routinely, because of (b)(4). Consequently, we do not recommend the company method as is, but some modification thereof. When a satisfactory dissolution test method is found, we would recommend eliminating the solubility characteristic test and replacing it with the dissolution test.

CHEMISTRY REVIEW NOTES
November 26, 1979

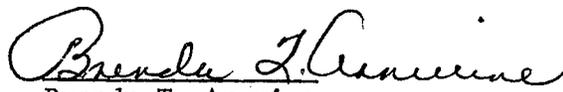
Re: Form 6 - #62-178
Griseofulvin Ultramicrosize Tablets
125 mg/tab and 250 mg/tab
Submitted by Ayerst Laboratories

Page 2

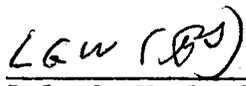
Since these tablets fulfill the current test requirements of 449.120d, perhaps it would be simplest to modify the monograph as to the dispersing medium and omit the specific (b)(4) used in the product.

Stability data are given on two lots of ultramicrosize griseofulvin powder under accelerated conditions (40°C/75% RH) for three months stored in amber glass bottles, metal screw caps and simulated warehouse containers. The moistures of both lots went up as high as (b)(4) from (b)(4)% for the material stored in the simulated warehouse containers. The moistures of the material stored in the amber glass bottles (b)(4). It would be good if the company reported the acceptable moisture range for this ultramicrosized griseofulvin powder so that we could make an evaluation of this stability data. Three batches of each dosage form of the tablets were included in a stability study under various temperatures, light and humidity conditions. The company is requesting a two year expiration date which appears to be satisfactory from the data presented.

The results of testing under 21 CFR 449.120d are satisfactory for each exhibit lot.


Brenda T. Arnwine
Antibiotic Chemistry Branch

Reviewed by


Lola G. Wayland
Chief, Scientific Evaluation Section
Antibiotic Chemistry Branch

No. of Tests - 81

Time Spent - 120 hours

 11/30/79

Following this page, 2 pages withheld in full - (b)(4)

Manufacturing and Controls Review

Antibiotic Form 6 #62-178 (449.120d)

Mfg.: Ayerst Laboratories
New York, New York

Application Date: August 30, 1979; Amended 2-20-80 and 3-10-80

Drug: Griseofulvin ultramicrosize 125 mg. and 250 mg.

1. Components:

(a) Griseofulvin (b)(4) - supplier: (b)(4)

(b) Manufacturing Procedure

(b)(4)



2- Manufacturing and Control Review

#62-178

2. Maximum batch size:

(b) (4) - 125 mg. or 250 mg. tablets.

3. Manufacturing, Processing and Packaging:

(a) Manufacturing, processing procedures - satisfactory

(b) Final product specifications - satisfactory subject to monograph revision

(c) Packaging

Bottle - HDPE white, opaque

Closures - child resistant or metal screw cap with (b) (4) liner

Blister package - polyvinyl chloride with aluminum foil back

Contract Packagers - (b) (4)

4. Laboratory Facilities:

In-plant - satisfactory

5. Stability Data:

(a) Ultramicrosize griseofulvin powder

Firm submitted accelerated data on two batches of the powder stored at 40°C - 75% R.H. for 3 months. In-house expiration date proposed - 2 years.

(b) Ultramicrosize griseofulvin tablets

Firm submitted accelerated data on two batches of the tablets stored in HDPE bottle at 62°C, 51°C, 40°C - high humidity - for 3 months.

6. Expiration date authorized:

24 months

7. Labeling:

Draft labeling

- FPL - 3-10-80 - Satisfactory
Plan

8. Inspection Reports:

Requested 1/28/80 - Satisfactory 2/5/80 HFD-332

3- Manufacturing and Control Review

#62-178

9. NCAA Report:

- (a) The exhibit batches conformed to the requirements of the official monograph (449.120d).
- (b) Ayerst proposed a dissolution test to replace the "solubility characteristic" test. Details of the proposed dissolution test will have to be resolved between NCAA and Ayerst.

10. Monograph Requirements:

The official monograph will have to be revised to provide for this tablet.

Areas of variance are:

- 1) The griseofulvin used in the tablet should be griseofulvin microsize. Ayerst uses griseofulvin " (b) (4) "
- 2) The griseofulvin should be dispersed in polyethylene glycol 6,000. the griseofulvin is not so dispersed in the Ayerst tablet.
- 3) The monograph provides for a solubility charactersitic test to distinguish between microsize and ultramicrosize tablets. Ayerst proposes to replace this test with a dissolution test.

11. Bioavailability Report:

Satisfactory 2/4/80

Comments: Form 6 is complete - drug may be "released".

Recommendation:

Approved

W. E. Magner
William E. Magner
3/12/80

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62-178

BIOEQUIVALENCE REVIEWS

Grisactin, Tablets
Ultramicrosize, 250 mg
FORM 6, 62-178

Ayerst Laboratories
685 Third Avenue
New York, New York
Submission Dated:
September 11, 1978

REVIEW OF A BIOAVAILABILITY PROTOCOL

Griseofulvin is obtained by fermentation of species of penicillium, and is indicated as an antifungal agent.

OBJECTIVES:

To compare the blood levels of Grisactin, Ayerst, ultramicrosize; to Gris-Peg, Dorsey and Grisactin, Ayerst, microsize.

PROTOCOL:

This is a three-way crossover design study, using 21 male subjects, between 18-50 years of age, within +10% of the ideal weight table, screened for any history of serious diseases and adequately tested clinically. Subjects will be free from other medication for 2 weeks. Subjects will fast for 12 hours before and 4 hours after dosing. Blood samples (10 ml) will be drawn in Vacutainers at 0, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 12, 24 and 48 hours. Plasma will be separated, frozen and assayed by Dept. of Pharmacy, Ayerst Labs, Rouses Point, N.Y., by a TLC-Fluorometric procedure. All subjects will sign Informed Consent Forms. Subjects will receive Gris-Peg, Dorsey 2 x 125 mg tablet, Grisactin, Ayerst, 500 mg tablet or Grisactin, Ayerst ultramicrosize 250 mg tablet with 100 ml of water, and separated by one week.

COMMENTS:

1. The principal investigator should be identified and his curriculum vitae submitted. A full description of the clinical facilities should be included; and the site of the study.
2. The source of the volunteers should be specified.
3. The lot numbers should be recorded, and the drugs assayed for content uniformity and dissolution rates.

4. A detailed description of the analytical procedures should be submitted with validation data to assure that the method has the required sensitivity, linearity and specificity to measure the drug and/or metabolites expected in the clinical specimens. This should include recovery data, standard curves, etc.

5. An informed consent form should be signed by all volunteers who participate in the study.

RECOMMENDATIONS:

The firm should be notified of our comments, and submit a revised protocol incorporating these comments before the study is initiated.

Joseph J. McGuire
Joseph J. McGuire
Biopharmaceutics Review Branch

cc: FORM 6 Orig., HFD-530 (3 copies), HFD-522, HFD-525, Chron File

JJMCGUIRE/mr/10/18/78

RD INITIALED BY SVDIGHE

FINAL TYPE INITIALED BY

SVD

10/18/78

Griseofulvin Tablets, 250 mg
Form 6, 62-178

Ayerst Labs.
685 Third Ave.
New York, N.Y. 10017
Submission Dated:
January 18, 1979

REVIEW OF BIOAVAILABILITY PROTOCOL

Griseofulvin is derived from penicillium, it is ultramicrosize crystals, and is indicated for the treatment of ringworm infections, and the related fungi.

OBJECTIVES:

To compare the blood levels of griseofulvin ultramicrosize after administering of Griseofulvin, 250 mg tablets mfg. by Ayerst to Fulvicin P/G mfg. by Schering in a single dose study and a steady state study.

PROTOCOL:

This is a two-way crossover design study, using 16 male subjects, between 18 to 5 years of age, within $\pm 10\%$ of the desired weight table, screened for any history of serious diseases and adequately tested clinically. Subjects will be free from controlled release anti-effective drugs for 30 days and all other medication for 2 weeks. Subjects will fast for 10 hours before dosing and 4.5 hours after closing. Subjects will receive a single dose of 250 mg tablet of griseofulvin, Ayerst or 250 mg Fulvicin Schering with 100 ml of water according to the following schedule:

Day		Blood Samples drawn at
Day 1		
	7:00 AM dose	7, 8, 9, 10, 11 AM
	7:00 PM dose	1, 3, 7 PM
Days 2 - 8		
	7:00 AM dose	7:00 AM
	7:00 PM dose	
Day 9		
	7:00 AM dose	8, 9, 10, 11 AM
		1, 3, 7 PM
Day 10	--	7 AM - 7 PM
Day 11	--	7 AM

A nine day washout period will be observed, and then the same schedule will be followed. Blood samples will be centrifuged, the plasma separated, frozen and sent to:

Mr. [REDACTED] (b) (6)
Biopharmacy Section
Ayerst Research Center
64 Maple Street
Rouses Point, New York 12979

The assay procedure will be a TLC-Fluorimetric method with a limit of detection of 20 ng/ml. The study will be submitted to the Institutional Review Board for approval. Subjects will sign an Informed Consent Form. The Clinical Investigator has not been chosen, nor the site of the clinical facilities. The clinical specimens will be assayed by Ayerst Research Labs, Rouse Point, N. Y.

COMMENTS:

1. The test and reference drug should be assayed for content uniformity and dissolution rates. The lot numbers should be recorded and the test drug should be from a production batch.
2. A detail description of the analytical methodology should be submitted, with data to demonstrate that it has the required sensitivity, linearity and specificity to measure the drug/and or metabolites expected in the clinical specimens when performed by the laboratory doing the assays.
3. The Informed Consent Forms, the C.V. of the clinical investigator and the site of the clinical laboratory should be submitted.
4. The firm has not described the methods, procedures and calculations for the single dose study. The justification and derivation for the equation:

$$AUC_{-48-} = \frac{Cp_{48}}{B} = \frac{\text{Plasma Conc. at 48 hr.}}{\text{Overall elimination rate}} \quad 0 \text{ const.}$$

should be submitted.

RECOMMENDATIONS:

The firm should be notified that the information for comments 2, 3, 4 should be submitted before the study is initiated.

Joseph J. McGuire
Joseph J. McGuire
Biopharmaceutics Review Branch

*This review was received by
HFD-531 on 10-15-79. The
study has been completed and the
results sent to HFD-522 on
9-7-79. The recommendations by*

cc: Form 6 Orig., HFD-530, HFD-522, HFD-525, Chron File HFD-522 are
after the fact at this
point in time.

JJMCQUIRE/mrs/2/28/79 (2370A)
RD INITIALED BY SJD

WEM

Griseofulvin (Grisactin Ultra)
250 (ultramicrosize) Tablet
Form 62-178

Ayerst Laboratories
New York, N.Y.
Submission Date
August 30, 1979

REVIEW OF A BIOEQUIVALENCY STUDY

The firm has submitted two studies to demonstrate the bioequivalency of a new griseofulvin ultramicrosize product, (Grisactin Ultra) compared to Gris-Peg (Dorsey). Gris-Peg is an ultramicrocrystalline solid-state dispersion of griseofulvin in polyethylene glycol 6000.

Purpose:

To investigate the bioequivalency of a new experimental ultramicrosized griseofulvin tablet compared to the reference drug product, Gris-Peg, Dorsey brand of griseofulvin (ultramicrosize) and Grisactin, Ayerst brand of griseofulvin (microsize).

RECOMMENDATION:

This bioequivalency study has demonstrated the bioequivalency of Grisactin-Ultra 250 mg tablet compared to Gris-PEG (2 x 125 mg) tablet. This new ultramicrosize formulation has also been found to be equivalent to Grisactin (microsize), 500 mg. However this latter equivalency presents a problem in that dose proportionally between the 250 mg and the 500 mg formulation has not been demonstrated (See Comment 2). Therefore, it is recommended that the labeling of the Gris-PEG and all ultramicrosized formulation be reviewed.

STUDY DESIGN:

Report 11, 602-22

Healthy male volunteers (N = 21) between 18 and 50 years and 145 to 185 pounds and within + 10% of the normal weight for their height and weight. Good health was ascertained by medical history, complete physical examination, routine clinical laboratory examination, electrocardiogram, and chest X-ray. No subject received a long acting anti-infective medication for 30 days preceding the study and no other drug for 14 days before the study. Subjects who were known to abuse alcohol or drugs, who were hypersensitive to griseofulvin or penicillin, and who had chronic liver problems were excluded from the study. Written informed consent was obtained from each subject.

Each subject was orally administered the following drug treatments in a randomized 3-way crossover design:

- A. Griseofulvin (ultramicrosized) Formulation No. S.P. 27841, Batch No. 1 LGE, 1 X 250 mg Tablet
- B. Griseofulvin (Gris-Peg, Dorsey), Batch No. C87639, 2 X 125 mg Tablet
- C. Griseofulvin (Grisactin, Ayerst microsize), Formulation No. M.P. 444, Batch No. 1KEQ, 1 X 500 mg Tablet

All medication were taken with 100 ml of water. The wash-out period between treatment was 7 days. No food, beverage or smoking was allowed for 4 hours post-dosing.

Blood samples (10 ml) were collected at 0, 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 hours after dosing. Plasma was harvested and frozen until assays could be conducted at Ayerst Laboratories, Rouses Point, N.Y. The method of analysis for griseofulvin was by a TLC-Fluoremetric procedure with a limit of detection of 25 ng/ml based on a 1.0 ml of plasma sample.

This study was conducted in the metabolic ward at Techni-Med Consultants, Inc., Wyncote, PA under the clinical direction of Carolyn Crawford, M.D.

RESULTS:

Table 1 gives the mean plasma levels from 0 to 48 hours after dosing with griseofulvin (ultramicrosize, Ayerst,) 250 mg, Gris-Peg, 2 X 125 and Grisactin (Ayerst) 500 mg. This Table also gives the mean peak plasma concentration (C_{max}) area under the plasma level vs-time curve and the time to peak (T_{max}).

Table 1

Time	Griseofulvin (Ultramicrosized)	Gris-Peg	Grisactin
	Ayerst 1 X 250 mg	Dorsey 2 X 125 mg	Ayerst 1 X 500 mg
1	.41 (46)*	.32 (50)	.36 (59)
2	.54 (35)	.52 (49)	.50 (43)
3	.58 (31)	.58 (42)	.54 (34)
4	.55 (39)	.54 (41)	.56 (31)
5	.56 (33)	.55 (45)	.57 (39)
6	.54 (34)	.49 (37)	.52 (40)
8	.50 (36)	.45 (31)	.51 (32)
12	.40 (33)	.40 (22)	.46 (30)
24	.23 (28)	.23 (44)	.27 (40)
48	.06 (71)	.05 (74)	.12 (62)
C_{max} , mcg/ml	0.69 (28)	.66 (31)	.64 (36)
T_{max} , hours	3.3	3.5	4.9
AUC, 0-24	9.57 (27.6)	9.16 (24.8)	10.12 (25.4)
AUC, 0-48	13.05 (24.6)	12.63 (24.9)	14.80 (25.3)

*Number in parenthesis denotes the coefficient of variation

No statistically significant difference among the three treatments were observed for peak levels. The time to peak for the Grisactin and the griseofulvin (ultramicrosized) was different at $p < .01$. There was no difference between the AUC, 0-24 hours, but the AUC, 0-48 hours for Grisactin was significantly greater ($p < .05$) than the ultramicrosized.

These results demonstrated that Gris-Peg and the newly formulated griseofulvin (ultramicrosized) were bioequivalent in terms of the AUC, 0-24 hours. Grisactin and griseofulvin (ultramicrosized) were not bioequivalent in terms of AUC, 0-48 hours. Twice the dose of griseofulvin (microsized) had a 14% greater AUC when compared to the griseofulvin (ultramicrosized).

STUDY 2

Report 11, 602-23

The second study was a bioequivalency study comparing a new production size batch of griseofulvin (ultramicrosized) Ayerst to Gris-PEG, Dorsey.

Healthy male volunteers (N = 16) between 18 and 50 years of age and between 145 and 185 pounds and $\pm 10\%$ of the ideal weight for their height and age were selected for this study. Good health was ascertained by medical history, physical examination, routine clinical laboratory examination, EKG and chest X-ray. The same criteria for exclusion from this study as the previous study. Written informed consent was obtained from each subject.

Each fasted subject (12 hours) was orally administered the following drug treatment in a randomized two-way crossover design:

- A. Griseofulvin, (ultramicrosized) Gris-PEG, Dorsey, 2 X 125 mg Tablet
- B. Griseofulvin (ultramicrosized), Ayerst, 1 X 250 mg Tablet

All medications were taken with 100 ml of water. The washout period between treatment was 7 days. No food, beverages, or smoking was allowed for 4 hours post-dosing.

Blood samples (10 ml) were collected at 0, 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 hours following drug administration. Plasma was harvested and frozen until assays could be conducted at Ayerst Laboratories at Rouses Point, N.Y. The method of analysis was a TLC-Fluoremetric procedure.

This study was conducted at Quincy Research Center, Kansas City, Mo. under the clinical direction of John Arnold, M.D.

RESULTS:

Table 2 gives the mean plasma levels of griseofulvin from 0-48 hours after dosing. The mean peak plasma levels, (C_{max}) time to peak (T_{max}) and the plasma AUC are also given in Table 2.

Table 2

Time (hours)	Gris PEG 2 X 125 mg	Griseofulvin (ultramicrosize) 1 X 250 mg
1	.30 (53)*	.31 (71)
2	.47 (39)	.49 (47)
3	.51 (28)	.57 (32)
4	.57 (21)	.58 (33)
5	.64 (18)	.61 (44)
6	.59 (20)	.56 (33)
8	.55 (23)	.52 (25)
12	.52 (12)	.47 (24)
24	.27 (36)	.25 (31)
48	.05 (103)	.06 (94)
C _{max} , mcg/ml	.70 (15)	.75 (34)
T _{max} , hours	4.8	6.3
AUC 0-24	10.56 (17)	10.21 (20)
AUC 0-48	14.79 (18)	13.95 (21)
AUC 0-00	16.19 (25)	15.35 (23)

*Number in parenthesis denotes the coefficient of variations

No statistical difference between the two treatments were observed for peak levels, time to peak, and AUC, 0-48 hours. These results indicate that Gris-PEG (2 x 125 mg) and griseofulvin (ultramicrosize), 250 mg were bioequivalent.

COMMENTS:

1. Validation of the TLC-fluorometric method did not include a standard curve no recovery information. The firm should be requested to furnish this information.
2. Present labeling for Gris-PEG indicates that "Gris-PEG Tablets differ from griseofulvin (microsize) tablets USP in that each tablet contains 125 mg of ultramicrosize griseofulvin biologically equivalent to 250 mg of microsize griseofulvin." Information from an FDA contract (No. 223-77-3011) on the Bioavailability of Griseofulvin conduct at the University of Tennessee under the direction of Marvin Meyer, Ph.D., indicates that this labeling claim is in error because the 500 mg Grisactin tablet did not demonstrate "dose proportionality" to the 250 mg Grisactin tablet.

It should be noted that Dorsey Laboratories (innovator) received approval for the label claim stated above for Gris-PEG in 1974. The firm demonstrated that 2 X 125 mg Gris-PEG tablets were bioequivalent to 500 mg Grisactin tablet but only about twice for 4 X 125 mg Gris-PEG with regards to C_{max} and AUC. Moreover, the AUC for Grisactin (500 mg) was only 1.5 times Gris-PEG (4 X 125 mg).

In a recent study submitted by Dorsey Laboratories, it was demonstrated that the 125 mg Gris-PEG was not be equivalent to 250 microsize (Grisactin, Ayerst, or Fulvicin V/F, Schering) 250 mg. These 250 mg formulations were found to be bioequivalent to each other.

These studies have demonstrated the Griseofulvin ultramicrosize may not be twice as available as the microsize griseofulvin. The explanation to this dilemma is the Grisactin (microsize) 500 mg tablet, which has generally been utilized as the reference standard compared to 2 X 125 mg ultramicrosize griseofulvin. When Grisactin 250 mg was utilized as the reference standard, bioequivalency was not observed. Dr. Meyer's studies have clarified this dilemma by demonstrating that there was not dose proportionality between the Grisactin 250 and 500 mg and the 500 mg Grisactin dose was less than 80% of the 250 mg formulation.

Charles M. Ise

Charles M. Ise, Ph.D.
Biopharmaceutics Review Branch

cc: Form 6, 62-178 Orig. HFD-530 (3), HFD-522 (Dr. Ise), Drug File
Review File, Chron File

CMISE/jmm/2/4/80 (3272P)

RD INITIALED BY SVDIGHE

FT INITIALED BY CMISE

C. M. Ise

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-178

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

6
Harrison
62-178

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

September 11, 1978

John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: BIOAVAILABILITY PROTOCOL FOR ULTRAMICROSIZED GRISEOFULVIN.

Dear Mr. Harrison:

We are submitting four copies of a proposed protocol for a bioavailability study for an ultramicrosize griseofulvin tablet. The Ayerst 250 mg tablet will be compared against the reference product 2 x 125 mg Gris-Peg® and against a microsize griseofulvin tablet 500 mg.

We would appreciate your expediting a review of this protocol with the Division of Biopharmaceutics for any comments.

Sincerely,

Carol E. Smith

for/ Henry S. Perdue, Ph. D.

HSP
CES/mf

RECEIVED
SEP 14 2 31 PM '78
FDA/BD/HFD-535

004584

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Chief
Biopharmaceutics Review Branch (HFD-522)

DATE: September 18, 1978

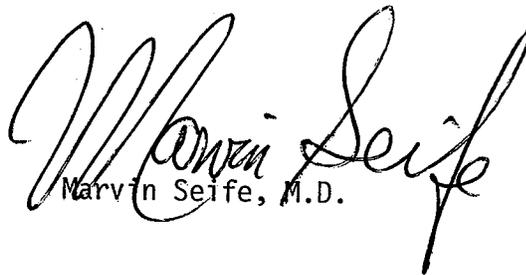
FROM : Director
Division of Generic Drug Monographs

SUBJECT: Griseofulvin (ultramicrosize) Tablets Form 6 #62-178

Sponsor: Ayerst Laboratories
New York, New York

Ayerst Laboratories proposes to request certification for a 250 mg. ultra-microsize griseofulvin tablet. Attached is a proposed protocol for carrying out a bioavailability study to compare Ayerst's new product to Dorsey Labs. "Gris-Peg".

Please review and comment whether the proposed protocol is satisfactory for generating the type of bioavailability data needed to satisfy our Form 6 requirements.


Marvin Seife, M.D.

Attachment



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

October 23, 1978

Our reference:
62-178

Henry S. Perdue, Ph.D.
Vice-President, Regulatory Affairs
AYERST LABORATORIES
685 Third Avenue
New York, New York 10017

Dear Dr. Perdue:

This is in reference to the proposed protocol submitted September 11, 1978, for a bioavailability study for an ultramicrosized griseofulvin tablet. Your proposed protocol was referred to our Biopharmaceutics Review Branch and the following comments have been made:

1. The principal investigator should be identified and his curriculum vitae submitted. The site of the study should be given, and a full description of the clinical facilities should be included.
2. The source of the volunteers should be specified.
3. The lot numbers of the products to be used in the test should be recorded, and the drugs assayed for content uniformity and dissolution rates.
4. A detailed description of the analytical procedures should be submitted with validation data to assure that the method has the required sensitivity, linearity, and specificity to measure the drug and/or metabolites expected in the clinical specimens. This should include recovery data, standard curves, etc.
5. An informed consent form should be signed by all volunteers who participate in the study.

Please submit a revised protocol incorporating the above comments before the study is initiated.

2- Henry S. Perdue, Ph.D.

62-178

We have reserved file number 62-178 for your forthcoming Antibiotic Form 6 for ultramicrosize griseofulvin tablets. Please include this file number on future correspondence pertaining to the ultramicrosize griseofulvin tablets.

Sincerely yours,

John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs

cc:
HFD-535
HFD-535/OD
HFD-430/Tab.
JDHarrison:hb



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

A-6
~~Harrison~~
File - no reply
needed.
J. Garrison
11/17/78

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

November 9, 1978

John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: File Number 62-178 - Ultramicrosize Griseofulvin Tablets

Dear Mr. Harrison:

Reference is made to your letter of October 23, 1978 concerning our proposed bioavailability protocol submitted to you September 11, 1978 for comment. We have noted your qualifications on the protocol and the following response is made to them.

1. "The principal investigator should be identified and his curriculum vitae submitted. The site of the study should be given and a full description of the clinical facilities should be included."

Dr. Carolyn S. Crawford will be the principal investigator of this study and her curriculum vitae is included. Also included are the curriculum vitae of the assistant investigators. The study will be conducted at Techni-Med Consultants, Inc. in Wyncote, Pennsylvania. These facilities encompass (b) (4) square feet in which there are two metabolic wards with beds for thirty volunteers. The facilities have a fully equipped kitchen, dining room, laboratory and shower facilities and a large area for recreation, i.e.; ping-pong, pool table, T.V. games, and shuffle board. They possess the necessary equipment and supplies for resuscitation and acute antidotal requirements.

2. "The source of the volunteers should be specified"

Free will volunteers are utilized such as students or employed or unemployed individuals.

3. "The lot numbers of the products to be used in the test should be recorded, and the drugs assayed for content uniformity and dissolution rates."

...../2

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FEDERAL BUREAU OF INVESTIGATION
U.S. DEPARTMENT OF JUSTICE
HFD-535
5388

The lot numbers of the drugs used in the study, in addition to content uniformity and dissolution rates, will be provided in the completed write up of the study.

4. "A detailed description of the analytical procedures should be submitted with validation data to assure that the method has the required sensitivity, linearity, and specificity to measure the drug and/or metabolites expected in the clinical specimens. This should include recovery data, standard curves, etc..."

The information requested in this comment will be provided in the completed write up of the study.

5. "An informed consent form should be signed by all volunteers who participate in the study."

All subject volunteers will sign an informed consent form prior to admittance of the study.

Sincerely,

Caral E. Smith

for Henry S. Perdue, Ph. D.

HSP
CES/mf



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

17-6
~~Harrison~~
Mr. Magner

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

January 18, 1979

John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: File No. 62-178 - Bioavailability Protocol for
Ultramicrosize Griseofulvin versus Competitor Products,
Single dose and Steady State Study.

Dear Mr. Harrison:

We are submitting four copies of a proposed protocol for a single dose and steady state study for an Ayerst ultramicrosize griseofulvin product. The Ayerst tablet will be compared against a Fulvicin P/6, Shering tablet. We request your comments on the design of the protocol.

At this time the principal investigator has not been determined, however, at the time of submission all proper information concerning the investigator and study site will be provided. Informed consent will be obtained from all volunteers. Lot numbers, content uniformity, dissolution rates, and analytical procedures will also be provided in the completed write up of the study.

We would appreciate your expediting a review of this protocol with the Division of Biopharmaceutics for any comments.

Sincerely,

Carol E. Smith

Henry S. Perdue, Ph. D.

RECEIVED
JAN 24 12 57 PM '79
FDA/BD/HFD-535

HSP
CES/mf

006273 for/

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DATE: January 24, 1979

TO : Jerome P. Skelly, Ph.D.
Biopharmaceutics Review Branch (HFD-522)

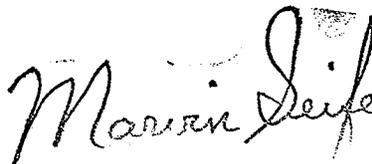
FROM : Director
Division of Generic Drug Monographs (HFD-530)

SUBJECT: Bioavailability Protocol - Form 6 #62-178 Griseofulvin (ultramicrosize) Tablets,
250 mg.

Sponsor: Ayerst Laboratories
New York, New York

The enclosed document is a resubmission of a protocol submitted to your office September 18, 1978, and reviewed by Dr. McGuire (10-18-78).

Please review and comment on the revised protocol.



Marvin Seife, M.D.

Enclosure

H-6
Harrison



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

August 30, 1979

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: Grisactin Ultra (griseofulvin ultramicrosize)
File Number 62-178

Dear Mr. Harrison:

We are submitting a Form 6 (in triplicate) for Grisactin Ultra (griseofulvin ultramicrosize) 250 mg and 125 mg Tablets.

As we have previously discussed, we are submitting griseofulvin (b)(4) raw material for certification and requesting that CFR Section 449.20 (a) (1) (ix) be waived. As the bulk (b)(4) griseofulvin raw material

(b)(4)
The raw material complies with all other monograph specifications.

Samples for griseofulvin (b)(4) raw material and griseofulvin ultramicrosize will be sent to you under separate cover.

As the present marketed products are described in the current monograph as being dispersed in PEG 6,000, and Grisactin Ultra does not meet this description, we would like to propose the monograph be amended to allow for our ultramicrosize product that is not dispersed in PEG 6,000. Grisactin Ultra tablets meet all the monograph specifications.

Two bioavailability studies were done against the reference product, Dorsey's Gris-Peg. The case reports from these studies are contained in Volumes 3, 4 and 5 of the set bound in blue folders. The results obtained in these studies show bioequivalence between Grisactin Ultra and the reference product.

RECEIVED
SEP 6 9 38 AM '79
FDA/BD/HFD-535

We trust the enclosed submission meets with the Administration's approval and look forward to an early response from you.

Sincerely,

Caral E. Smith

for/

Henry S. Perdue, Ph. D.

HSP
CES/mf



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

A-6
Harrison

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

August 30, 1979

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: Grisactin Ultra (griseofulvin ultramicrosize)
File Number 62-178

Dear Mr. Harrison:

We are submitting the following samples for certification.

Griseofulvin, (b)(4) Raw Material

Batches: G2718/78
G2759/78

Grisactin Ultra Tablets
(griseofulvin ultramicrosize)

Batches: K207 LGE
M238 LZN
410-80-1
A427 MFZ
410-82
410-80-2

RECEIVED
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FDA/BD/HFD-535

009828

As we have previously discussed, we are requesting that CFR Section 449.20 (a) (1) (ix) be waived for griseofulvin, (b)(4) raw material.

Protocols for these batches are enclosed.

Sincerely,

Carol E. Smith

for / Henry S. Perdue, Ph. D.

HSP
CES/mf

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Chief,
Biopharmaceutics Review Branch (HFD-522)

DATE: September 7, 1979

FROM : Director,
Division of Generic Drug Monographs (HFD-530)

SUBJECT: Bioavailability Study Form 6 #62-178

Griseofulvin Ultramicrosize Tablets 125 mg and 250 mg

Sponsor: Ayerst Laboratories
New York, New York

We have previously forwarded to your attention a couple of proposed protocols for bioavailability studies on this drug. A protocol submitted September 11, 1978 was reviewed and commented on by your office, however we have no record of your review or comments on a revised protocol (1-18-79) submitted to your office on January 24, 1979.

The firm has now submitted bioavailability studies to demonstrate their product is comparable to the reference drug (Dorsey's Gris-Peg). Please note that volumes 3, 4, and 5 consists of case reports. We are enclosing volume 3, if the other two volumes of case reports are considered necessary for your review please call HFD-535 (34340).

Please review and comment on the attached bioavailability study.

Marvin Seife, M.D.

Attachment

cc:

~~HFD-535~~

HFD-535/OD

HFD-430/lab.

HFD-530/Dr. Seife

WEMagner;hb

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 9-7-79
FROM: Marvin Seife, M.D.		OFFICE HFD-500
TO: Division of Biopharmaceutics HFD-520		DIVISION HFD-530
SUBJECT: Ajetst Labs.		
SUMMARY		
ATTENTION: Dr. Jerome P. Skelly		
FORM 6 - 62-178		
NDA #:		
PRODUCT: GRiseofulvin ULTRAMICROSIZED Tabs. 125 + 250 mg.		
Please review the dissolution data on the above drug. }		
Thank you,		
Wendy / MS		
Marvin Seife, M.D.		
SIGNATURE	DOCUMENT NUMBER	

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : HFD-430

DATE: September 7, 1979

FROM : HFD-535

SUBJECT: Griseofulvin ultramicrosize tablets 125 mg and 250 mg
Form 6-62-178 Sponsor: Ayerst Laboratories
New York, New York

We have enclosed a copy of a new Form 6 from Ayerst Labs which will provide for the batch certification of a griseofulvin ultramicrosize tablet. As you will note there are a few problems.

- a. The "used in" does not meet the monograph.
- b. The griseofulvin is not dispensed in polyethylene glycol.
- c. The cover letter states that the tablets will meet all the monograph specifications, however they do not propose to run the solubility characteristic test.
- d. You will probably come up with a few more problems which are not so obvious at this time.

At this time we really don't know which way to go - reinstate the bulk griseofulvin "regular" monograph, propose a new bulk monograph for griseofulvin ultramicrosize powder, propose a new monograph for this tablet or try and revise 449.120d to provide for this tablet.

A Form 6 number was assigned to this application because the submission first came in as a proposed protocol for a blood study. It wasn't until the application was submitted that we realized it may be a Form 5. If necessary we can change the numbers at a later date.

The firm has submitted samples of (b)(4) griseofulvin which we are forwarding to you, however we don't believe there is any need to run any tests on these samples. The material is from (b)(4) and it's the same griseofulvin that you have been looking at, except that Ayerst (b)(4) (b)(4) before they have been submitting it for certification. In addition, at this time we are of the opinion it would not be a good idea to reinstate the monograph for the (b)(4) material. As for "releasing" the griseofulvin, I don't believe our policy at this time is in harmony with providing for "releasing" an antibiotic substance.

Following your review of the application and testing of the samples we would appreciate your comments and suggestions as to how to best handle the monograph problems.

William E. Magner

Enclosures

1. copy of Form 6
2. copy of analytical data
3. samples

HFD-535
HFD-535/OD
HFD-430/lab.
WEMagner:hb

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Wm. Magner - HFD-535
CDRS

DATE: Dec. 5, 1979

FROM : Gordon G. Carter, Acting Deputy Director, NCAA
HFD-431

SUBJECT: AYERST GRISEOFULVIN ULTRAMICROSIZED TABLETS
FORM 62-178

The attached chemistry review notes present a very complete evaluation of this Form 6 application.

The exhibit lots conform to the requirements of 449.120d and are satisfactory. Supporting data for a two-year expiration date are adequate.

As noted on the second page of the review, the simplest approach appears to be to modify the existing monograph for the dispersing medium and omit the specific (b) (4) used in the product.

As for test procedures, the firm is proposing a dissolution test to replace the solubility characteristic test. We agree with the approach; however, we found the firm's dissolution method must be modified. The development of a satisfactory dissolution test would not appear to be difficult.

We would recommend the approval of this Form 6 application contingent on the development of an adequate dissolution test and the formulation of a modified 449.120d monograph to cover the product.


Gordon G. Carter

Att.

cc:
HFD-400
HFD-430/31
HFD-436 (2)
HFD-430 (RF)

GGCarter:bhp



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

December 18, 1979

Our reference:
62-178

Ayerst Laboratories
Attention: Henry S. Perdue, Ph.D.
685 Third Avenue
New York, New York 10017

Gentlemen:

This is in reference to your Form 6 submission of August 30, 1979 to provide for the batch certification of griseofulvin (ultramicrosize) tablets. Our laboratories have completed their review of the exhibit samples, we are forwarding their comments.

1. The results of the testing of the exhibit samples was satisfactory. All lots tested conform to the requirements of S449.120d.
2. As part of our testing of this product, we did the dissolution test submitted by the company. It employs the paddle method using sodium lauryl sulfate as the dissolution medium and (b) (4) in the analytical procedure. We found the dissolution medium to be satisfactory but using (b) (4) for the analysis would present problems if the method were used routinely, because of (b) (4). Consequently, we do not recommend the company method as is, but some modification thereof. When a satisfactory dissolution test method is found, we would recommend eliminating the solubility characteristic test and replacing it with the dissolution test.

As you know it will be necessary to revise the present monograph to accommodate your product. Our main consideration will be to provide for the use of griseofulvin which does not meet the specification for specific (b) (4) and for the dispersion of the griseofulvin in (b) (4).

2- Ayerst Laboratories
62-178

As noted above our laboratories are interested in the possibility of a dissolution test to replace the solubility characteristic test to distinguish between the microsize tablet and the ultramicrosize tablet. We suggest that your Pharmacy Research and Development people contact our laboratories with the goal of resolving the problems associated with the use of [REDACTED] ^{(b) (4)} in preparing the volumetric dilutions.

From the limited dissolution data submitted with the application it would appear that your dissolution rate method will distinguish between the microsize and ultramicrosize tablets. We would like to see considerably more dissolution data to reinforce this concept. Please submit comparative dissolution rate data between your 125 mg. ultramicrosize tablets and the products manufactured by Dorsey and Schering, and comparative data between the marketed microsize tablets of the same strength. Since your application provides for a 250 mg. ultramicrosize tablet, we suggest the same type of study between your 250 mg. tablet and Schering's.

It would of course be preferable if the above suggested studies could be conducted using a modified method (without [REDACTED] ^{(b) (4)}), however, if this is not possible at this time we suggest you conduct the studies using your current dissolution method.

We have assigned identification number 62-178 to this application. All future correspondence pertaining to this Form 6 should refer to this number and to antibiotic regulation 449.120d under which the drug is eligible for certification.

If we can be of further assistance in this matter, please feel free to contact this office.

Sincerely yours,

William E. Magner
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs

cc: HFD-436/LWayland
HFD-535
HFD-535/OD
HFD-430/lab.
WEMagner:hb

Hfd-535

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Division of Drug Manufacturing (HFD-320)
Associate Directorate for Compliance

DATE: January 28, 1980

FROM : Division of Certifiable Drug Review Staff (HFD-535)
Wm. E. Magner, ext. 3-4340

SUBJECT: GMP EVALUATION REQUEST

NDA/ANDA/IND # :
FORM 5/6 # : 62-178

DRUG: Griseofulvin Ultramicrosize Tablets

DRUG CLASSIFICATION: N/A PRODUCT CLASSIFICATION CODE: TCM

180 DAY DATE: N/A

APPLICANT: Ayerst Laboratories
Rouses Point, N.Y.

FACILITIES TO BE EVALUATED (Name, Address, & Operations to be performed for Applicant)

This firm has made griseofulvin tablets for a number of
years. We only need a current evaluation of their GMP status.

ADDITIONAL INFORMATION: _____

FOR HFD-320 USE ONLY

CONTROL #: _____

Date Received: _____

Date Completed: _____

cc: HFD-320 (original)
HFD-535 (2 copies)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 1-28-80
FROM: <i>McQueen</i>		OFFICE
TO: <i>Dave</i>		DIVISION
SUBJECT: <i>Draft labeling</i>		
<p data-bbox="224 409 324 430">SUMMARY</p> <p data-bbox="251 472 495 535"># 62-178</p> <p data-bbox="1153 430 1372 535">Ayerit N.Y. N.Y.</p> <p data-bbox="251 577 1291 682">Drug: Quisefokin with ampicillin Tablets -</p> <p data-bbox="365 724 1193 882">Please review the draft labeling in the attached Form 6.</p> <p data-bbox="998 1711 1307 1858">Dorsey 50-475</p>		
SIGNATURE <i>McQueen</i>	DOCUMENT NUMBER	

Joseph

Dr. MORRISON - Ayerst

1-30-80

Asked about his
application - I explained about
the hold up -

- ① No bioactivity report
- ② need fine printed labeling
- ③ need GMP stator from HFD-322

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Lola G. Wayland HFD-436

DATE: January 31, 1980

Thru: Dr. Joseph H. Graham HFD-430 _____
Director, NCAA

FROM : HFD-535

SUBJECT: Dissolution Testing - Griseofulvin Tablets

Please refer to the recent report (12/5/79) of your review of Form 6 #62-178. It appears from the work done on the Ayerst ultramicrosize griseofulvin tablets that their dissolution test method (with a little revising) might be a satisfactory alternative to the solubility characteristic test. Information from Ayerst and the preliminary work done by your section indicates that Ayerst dissolution test method will distinguish between griseofulvin tablets and ultramicrosize griseofulvin tablets.

It is our understanding that Ayerst understands the problem and hopefully either Ayerst or NCAA will come up with a suitable substitute for the (b) (4) or whatever is necessary to take care of the problem.

Since more work will be required on the dissolution test method and confirmation necessary to insure that the method will distinguish between all the griseofulvin tablets and ultramicrosize griseofulvin tablets on the market we have requested samples from all the suppliers. We have enclosed samples with cover letters from the following manufacturers.

- (1) Dorsey - 3 samples
- (2) McNeill - 2 samples
- (3) Schering - 3 samples

If the problems with the method can be resolved and the method is satisfactory to distinguish between the regular and the ultramicrosize tablets we will initiate an action to revise monograph 449.120d.

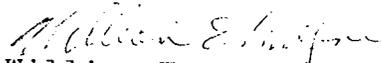
cc:

HFD-535

HFD-535/OD

HFD-430/Dr. Graham

WEMagner:hb


William E. Wagner

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director
Division of Certifiable Drug Review Staff DATE: 2/5/80
~~Drug Products~~, HFD-535
Attn: Wm. E. Magner

FROM : Chief, Manufacturing Review Branch, HFD-322
Division of Drug Manufacturing

SUBJECT: Approvable (~~ANDA/ND~~) Form 6

62-178 Griseofulvin Ultramicrosize Tablets

Applicant/Manufacturer: Ayerst Laboratories - Profile
Rouses Point, N. Y. 8/31/79
Satisfactory

We have evaluated the operations of Ayerst Laboratories, Rouses
Point, New York

as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) for the subject pending application (X). We conclude that there is no reason to withhold approval of the subject application (S) insofar as CGMP compliance of this/these firm(s) is concerned for the type of operations as specified in this/these pending application(s).

Our evaluation is based in part on Establishment Inspection and Quality Assurance Profile information as referenced above.

Walter A. Brown
for David H. Bryant

Bruce E. Byer
2/5/80

HFD-332
cc: BUF-DO (HFR-2250)
HFD-322 Firm File
HFD-300 R/F
HFD-535 (~~ANDA/ND~~) Original
Form 6



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

AL
Magner

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

February 20, 1980

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: Grisactin^(R) Ultra (griseofulvin ultramicrosize)
File Number 62-178

Dear Mr. Harrison:

Reference is made to our August 30, 1979 Form 6 for 250 mg and 125 mg griseofulvin ultramicrosize tablets and to correspondence of December 18, 1979 from Mr. William E. Magner of the Administration concerning our August 30th submission. Mr. Magner, in his letter of December 18, 1979, requested additional data which would demonstrate that the dissolution method included in our August 30th submission would distinguish between the microsize and ultramicrosize tablets.

We are submitting at this time, in triplicate, data on Ayerst, McNeil, Schering, and Dorsey products which demonstrate the suitability of the Ayerst dissolution method. Dissolution of griseofulvin tablet products using Method 1D0513 was determined for sample lots of Ayerst and three other manufacturers of ultramicrosize and microsize griseofulvin dosage forms. Individual data on each of 6 tablets for each lot tested with a calculated mean and coefficient of variation (CV%) are given in EXHIBIT 1. These data are also presented in the attached graphs. In addition to these data, additional supporting data is provided in EXHIBIT 2.

These data indicated that the Ayerst dissolution procedure can reproducibly discriminate between tablets containing microsize or ultramicrosize griseofulvin. The method appears to be applicable for testing not only Ayerst griseofulvin products but other manufacturers' products as well.

The data on Ayerst products also support the following Ayerst dissolution specifications:

- Microsize Tablets: Not less than (b) (4) dissolved in 30 minutes
- Not less than (b) (4) dissolved in 30 minutes
- Ultramicrosize Tablets: Not less than (b) (4) dissolved in 30 minutes
- Not less than (b) (4) dissolved in 60 minutes

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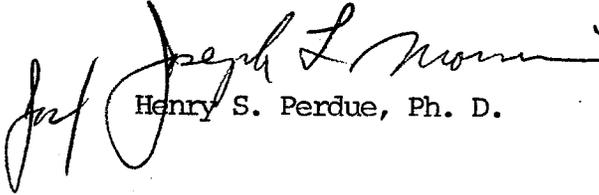
We are also providing an updated stability report. Twelve week stability data were submitted in our Form 6 application dated August 30, 1979. We are now providing 6 month and 12 month data on griseofulvin ultramicrosize. These new data, along with a copy of the original reports submitted on August 30, 1979 can be found in EXHIBIT 3.

Evaluation of the suitability of solvents other than (b) (4) to avoid potential problems in an automated dissolution method is in progress. The results of this evaluation will be submitted at a later date.

We trust that this information will permit a rapid completion of the review of our August 30th submission

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331 (j).

Sincerely,



Henry S. Perdue, Ph. D.

HSP
JLM/mf

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : HFD-435
Attention: Lola Wayland

DATE: February 26, 1980

FROM : HFD-535

SUBJECT: Ultramicrosize griseofulvin tablets - Dissolution Test
Form 6 #62-178

Sponsor: Ayerst Labs.
New York, N.Y.

On January 31, 1980, we sent you some samples from the various manufacturers of griseofulvin tablets.

Ayerst has now amended their pending application to provide additional information on their dissolution method. The enclosed information in conjunction with your work on samples previously provided should help in making a determination as to the suitability of their method.

William E. Magner

Attachment

cc:

HFD-535

HFD-535/OD

HFD-430/lab.

WEMagner:hb

MEMO OF MEETING February 27, 1980

Members Present:

Dr. Marvin Seife (HFD-530)
Dr. Raymond Barzilai (HFD-530)
Dr. Shrikant Dighe (HFD-522)
Dr. Keith Rotenberg (HFD-525)
Mr. John Hunt (HFD-525)
Mr. John D. Harrison (HFD-535)
Mr. William E. Magner (HFD-535)

Subject:

Labeling of Griseofulvin Ultramicrosize Tablets

Products involved:

Gris-Peg (ultramicrosize) Dorsey Form 5	#50-475
Fulvicin P/G (ultramicrosize) Schering Form 6	#61-996
Grisactin Ultra (ultramicrosize) Ayerst Form 6	#62-178 (Pending)

On the basis of bioavailability data submitted in 1974, which indicated that Gris-Peg is about twice as bioavailable as Grisactin (Ayerst), the Dorsey product was approved with labeling which states that "each tablet contains 125 mg. of ultramicrosize griseofulvin biologically equivalent to 250 mg. of microsize griseofulvin".

Within the last year or so other bioavailability studies seem to indicate that this may not be true. A study done under FDA contract (223-77-3011) at the University of Tennessee indicated that the Ayerst microsize griseofulvin 500 mg. tablets is not dose proportional to their 250 mg. microsize capsules, also, that the ultramicrosize products tested were not bioequivalent to microsize products based on labeling claims. A study done by (b) (4) in 1977 ("study (b) (4)") indicated that Gris-Peg was only 33% more bioavailable than Ayerst's griseofulvin microsize tablet. A submission by Dorsey dated June 30, 1978, to provide for (b) (4) (b) (4) and a new 250 mg. ultramicrosize tablet indicated that the test drugs when compared to Grisactin Tablets (500 mg.) were only about 65 to 79% more bioavailable.

In the opinion of HFD-525 and HFD-522 there is ample evidence to support our position that the current approved labeling for griseofulvin ultramicrosize tablets has not been adequately substantiated; however, before the involved firms are notified of our position it was agreed that the original Dorsey submission of 1974 would be subject to re-review. That study is now in Federal Storage. In the middle of January a request was made to retrieve these documents, however as of this date they have not been received.

It was agreed that the recently reviewed Ayerst study satisfactorily demonstrated that their griseofulvin ultramicrosize tablet is bioequivalent to the Dorsey product, therefore Ayerst's application will be approved with the understanding that the labeling is under review and revisions may be necessary in the future.

It was also decided that the Dorsey submission of June 30, 1978, providing for [REDACTED] (b)(4) and a new 250 mg. tablet was satisfactory and their submission is subject to approval pending the outcome of one additional study currently under review by HFD-525.

The general concensus among members at this meeting was that the griseofulvin ultramicrosize tablets on the market or provided for in pending applications are bioequivalent, however the current labeling statement that the efficiency of gastrointestinal absorption of ultramicrosize griseofulvin is approximately twice that of conventional microsize griseofulvin is probably not true.

Enclosure - Summaries of recent Dorsey submissions.

William E. Magner

Following this page, 5 pages withheld in full - CCI (b)(4)

memo for the file

2-29-80

Telephone Conversation

Dr. Morrison of Ayerst Labs called to ask if we had made any decision concerning the approval of their generic tablet application. I told him that we had a meeting with Drs. Seife and HFD-525 and HFD-522, and a decision was made to approve the Ayerst application and resolve the labeling problem with generic tablet application at a later date.

He told me about a typographical error on page one of the cover letter for the February 20, 1980 submission. Entry under dissolution data - micro size tablet, should read "not less than (b)(4) % dissolved in 60 minutes."

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : HFD-140
Attention: Mrs. Joan Eckert

DATE: March 3, 1980

FROM : HFD-535

SUBJECT: Revision- Monograph 449.120d Form 6 #62-178 Griseofulvin (ultramicrosize) Tablet

Sponsor: Ayerst Laboratories
New York, New York

The subject firm has submitted a Form 6 for a griseofulvin ultramicrosize tablet which meets the potency and other tests under monograph 449.120d, however their tablet differs from the monograph as follows:

- (1) The Ayerst tablet is not dispersed in polyethylene glycol 6,000.
- (2) The griseofulvin used in making the tablet is not griseofulvin microsize. The Ayerst "used in" meets all the requirements of 449.20 accept (b) (4).

Please revise monograph 449.120d to provide for the Ayerst tablet. The Ayerst application is approvable on our receipt of final printed labeling.

William E. Magner

cc:
HFD-535
D-535/OD
HFD-430/lab.
WEMagner:hb



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

AL
27 Magnu
14 Harrison

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

March 3, 1980

No reply
necessary
Permu
3-13-80

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: Grisactin^(R) Ultra (griseofulvin ultramicrosize)
File Number 62-178

Dear Dr. Harrison:

Reference is made to our submission dated February 20, 1980 which was personally delivered to the Administration on February 22, 1980. This submission contained additional dissolution and stability data for our ultramicrosize griseofulvin product as requested by Mr. Magner of the Administration.

We wish to bring to your attention a typographical error which appears at the bottom of the first page of the cover letter. The Ayerst dissolution specifications for the microsize tablets should read:

Not less than (b)(4) % dissolved in 30 minutes
Not less than (b)(4) % dissolved in 60 minutes

rather than:

Not less than (b)(4) % dissolved in 30 minutes
Not less than (b)(4) % dissolved in 30 minutes

Please correct the Administration's copies of the February 20, 1980 submission.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331 (j).

Sincerely,

Henry S. Perdue
Henry S. Perdue, Ph. D.

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and 23.6% of "unit observations" of the product were at or below the MAC. "This, by any stretch of the imagination, does not indicate the product is widely and consistently available," Dorsey argued.

Dorsey requested time to make a presentation at the next meeting of the PRB board, scheduled for March 12-13. The company said it was bringing "a practicing MD" to "offer a factual, real world perspective of the various consequences, from the patient's and MD's perspective, of implementing the MAC on potassium chloride 10% liquid as proposed."

¶ The MAC could have a "devastating impact" on patient compliance during long-term therapy by reducing "flavor options via various product brands" to a "negligible level," Dorsey predicted. The salty taste of the drug "is extremely difficult to mask," leading to "taste fatigue of flavored products... on a frequent basis," the company added. Use of potassium chloride in concomitant therapy for diseases such as hypertension and congestive heart failure makes patient compliance "crucial," with non-compliance leading to possible additional visits to the MD, "and even hospitalization with resultant increased costs to other health-related budgets," Dorsey added.

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SCHERING FULVICIN 500 MG SUPERIOR BIOAVAILABILITY v. Ayerst's *Grisactin* and other 500 mg griseofulvin products indicates "a significant bioavailability disparity" among the drugs which "makes the establishment of a MAC at this time inappropriate," Schering maintained in Feb. 22 comments on HEW's proposed reimbursement limit ("The Pink Sheet" Jan. 28, p. 11). However, Schering added, if the Pharmaceutical Reimbursement Board (PRB) "is convinced that a MAC must be established, it is clear that *Schering's* drug should be the reference standard used since it has the most significant bioavailability of all currently marketed forms."

The Fulvicin mfr. cited results of an FDA contract study at *UTenn* comparing bioavailability of all griseofulvin dosage forms. Results of the study "clearly demonstrate that Schering's Fulvicin is significantly better absorbed into the blood serum than is *Grisactin*," Schering declared. In clearing the 500 mg form for a MAC, FDA asserted the study showed all marketed products to be bioequivalent.

¶ "For example," Schering explained, "the plasma levels obtained at one hour, two hours, three hours, four hours, six hours, eight hours, and 10 hours are significantly higher for Fulvicin 500 mg as compared with *Grisactin* 500 mg. In addition, the peak plasma concentration shows a 23.9% difference in favor of Fulvicin over *Grisactin*. Further, the area under the level-time curve... shows a difference of 17% in favor of Fulvicin. This difference is statistically significant."

¶ The *UTenn* investigators recommended that Schering's 500 mg and 250 mg products be the reference standard, Schering said. The mfr. quoted the investigator's report which noted Fulvicin "exhibited the best bioavailability of all" and concluded "these two dosage forms would appear to be better suited as reference products than the suspension dosage form." Schering told the PRB it intended to discuss the study further at the March 12-13 hearing on the proposed MACs.

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PHENYTOIN LABEL CAUTION Re REVERSIBLE LYMPH NODE HYPERPLASIA by FDA's Peripheral and CNS Drugs Advisory Cmte.,

at its Feb. 23 meeting. A full report...



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Rec. 3/10/80
AL
Magner

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

March 10, 1980

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: Grisactin^(R) Ultra (griseofulvin ultramicrosize)
File Number 62-178

Dear Mr. Harrison:

Reference is made to our August 30, 1979 Form 6 for 250 mg and 125 mg griseofulvin ultramicrosize tablets. We included in our August 30th submission draft labeling for the subject drug.

We are submitting at this time final printed labeling for this product. We trust that this will now permit a rapid approval of our submission.

Sincerely,

for / Joseph L. Monahan
Henry S. Perdue, Ph. D.

HSP
JLM/mf

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FDA/BD/HFD-535

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER **62-178**
DATE APPROVAL LETTER ISSUED
3/13/80

TO: Press Relations Staff (HFI-40)

FROM: Bureau of Drugs
 Bureau of Veterinary Medicine

ATTENTION
Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: ORIGINAL NDA SUPPLEMENT TO NDA ABBREVIATED ORIGINAL SUPPLEMENT TO ANDA
CATEGORY: HUMAN VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG
Atiactin Ultra (griseofulvin + itraconazole)

DOSAGE FORM: **Oral - Tablet**
HOW DISPENSED: RX OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

**griseofulvin + itraconazole
125 mg x 250 mg Tablet**

NAME OF APPLICANT (Include City and State)
**Ayerst Laboratories
New York, N.Y.**

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Anti-fungal

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: **William E. Maguire**

DATE: **3-12-80**

FORM APPROVED BY

NAME: **Thomas S. Seife, M.D.**

DATE: **3/13/80**