

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 60-212

Name: Grisactin® (Griseofulvin) Tablets

Sponsor: Ayerst Laboratories

Approval Date: June 20, 1972

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 60-212

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 60-212

APPROVAL LETTER



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Hand del by Dr Swobas. 6-20-72 12/6/71 WTR/KP. AG Mager

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

December 6, 1971

Mr. William T. Robinson
Certification Services Staff
Division of Anti-Infective Drug Products
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Date Approved 6/20/72
Account No. _____
Signed [Signature]
For the Commissioner of Food and Drugs
Department of Health, Education and Welfare

Dear Mr. Robinson:

SUBJECT: NDA 60-212, GRISACTIN® (griseofulvin (microsize)) Tablets

As requested by the Administration we are submitting, in triplicate, an updated Form 6 for GRISACTIN® (griseofulvin (microsize)) Tablets. Consideration has been given to the recommendations appearing in your letter of October 1, 1971 and these have been incorporated into the enclosed Form 6.

(b) (4) is in the process of completing an Antibiotic Form 4 for shipment of (b) (4) griseofulvin to Ayerst Laboratories, Rouses Point, N.Y. When we have received the completed form, it will immediately be forwarded to the Administration. In addition, we are also in the process of obtaining up-dated Antibiotic Form 4's from (b) (4) and the (b) (4) of (b) (4). Again these will be forwarded to the Administration as soon as they have been completed.

A Form 8, allowing for the repackaging of GRISACTIN® (griseofulvin (microsize)) Tablets by the (b) (4) of (b) (4), was submitted to the Administration on (b) (4) and was approved on (b) (4). Repackaging Permit No. (b) (4) was assigned. Since this is already on file with the Administration we have not enclosed a copy herein.

In response to Item No. 3 of your October 1, 1971 letter, in process controls are contained in Parts 3f, 3g, 3h, 3n, and 3o of the enclosed Form 6.

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

Sincerely,

AYERST LABORATORIES

[Signature]

Henry S. Perdue, Ph.D.
Director, Regulatory Affairs



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 60-212

LABELING

6.

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



Labels glued on bottle.

Ayerst

GRISACTIN[®]
BRAND OF
GRISEOFULVIN
(MICROSIZED)

442,443,444 57

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 is produced by a special process that fractures griseofulvin particles into minute crystals of irregular shape offering a greater and more effective surface area for increased gastrointestinal absorption.

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.

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals mainly because of insolubility of the drug in aqueous media of the upper G.I. tract. The peak serum level found in fasting adults given 0.5 Gm. occurs at about four hours and ranges between 0.5 to 2.0 mcg./ml. The serum level may be increased by giving the drug with a meal with a high fat content.

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 sulphuratum

Trichophyton schoenleinii

Microsporum audouinii

Microsporum canis

Microsporum gypseum

Epidermophyton floccosum

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

The use of this drug is not indicated for

Microsporium gypseum
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 in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin, once a week, during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Usage in Pregnancy

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

Animal Reproduction Studies

It has been reported in the literature that griseofulvin was found to

**GRISACTIN® [griseofulvin
(microsize)] cont'd.**

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 penicillin, the possibility of cross-sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

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 rein-

with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

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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: 0.5 Gm. daily (125 mg. q.i.d., 250 mg. b.i.d., or 500 mg./day). Patients with less severe or extensive infections may require less, whereas those with widespread lesions may require a starting dose of 0.75 Gm. to 1.0 Gm. a day. This may be reduced gradually to 0.5 Gm. or less after a response has been noted. In all cases, the dosage should be individualized.

Children: A dosage of 10 mg./kg. daily is usually adequate (children from 30 to 50 lb., 125 mg. to 250 mg. daily; children over 50 lb., 250 mg. to 500 mg. daily, in divided doses). Dosage should be individualized, as with adults.

Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

HOW SUPPLIED

GRISACTIN [griseofulvin (micro-size)]—

GRISACTIN 125, each capsule contains 125 mg., in bottles of 100 (NDC 046-0442-81) and 500 (NDC 046-0442-85).

GRISACTIN 250, each capsule contains 250 mg., in bottles of 100 (NDC 046-0443-81) and 500 (NDC 046-0443-85).

GRISACTIN 500, each tablet (scored) contains 500 mg., in bottles of 60 (NDC 046-0444-60).

AYERST LABORATORIES
INCORPORATED

New York, N.Y. 10017

Available by arrangement with
IMPERIAL CHEMICAL INDUSTRIES
LIMITED

Revised September 1971.

PRINTED
IN
U.S.A.

1

AYERST LABORATORIES Pharmaceuticals Through Medical Research
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION



685 Third Avenue, New York, N. Y. 10017 • (212) YUKon 6-1000/ Cable: ALPHAMIN, New York

*OK to sign out
SPP 4/2/70*

March 30, 1970

Date 4-6-70

Repacking Patent No. (b) (4)

Mr. Robert C. Brandenburg
Director
Division of Certification Services
Department of Health, Education and Welfare
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Signed *RCB Brandenburg*
For the Commissioner of Food and Drugs
Department of Health, Education and
Welfare

1555

Dear Mr. Brandenburg:

Subject: NDA 60-212, GRISACTIN® (griseofulvin; microsize) Tablets,
500 mg., Physicians Complimentary Dispenser.

We are transmitting herewith, in triplicate, the final printed labeling for a physicians complimentary dispenser for this product. Please note the labeling has been revised to incorporate the suggestions of the Administration, as outlined at a meeting, between our Dr. Svokos and Mr. Powers of your office, in Washington on February 6, 1970.

We trust the Administration will find the labeling satisfactory and that an early approval is granted so that we may proceed with the preparation and distribution of this sample package as soon as possible.

Your help in expediting this matter would be most appreciated.

We should like the Administration to retain this information in its files for NDA 60-212.

Sincerely,

AYERST LABORATORIES

Henry S. Perdue for

Henry S. Perdue, Ph.D.
Assistant Director,
Regulatory Liaison

HSP:eb
SGS
Enc.

Grisactin[®] 500

Brand of
GRISEOFULVIN (MICROSIZE)

2 Tablets/PHYSICIAN'S COMPLIMENTARY PACKAGE/No. 444/GRISACTIN[®] 500/Each tablet (scored) contains 500 mg. griseofulvin (microsize)./CAUTION: Federal law prohibits dispensing without prescription.

444 Control No. 2ADV
Exp. Date Jan. '74



R_x

B0167-144-870

PRINTED IN U.S.A.

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**Some facts on
fungal skin
infections**

This booklet has been prepared especially to tell you something about fungus infections. It may help you to better understand your skin infection, and let you see why it is so important that you follow your doctor's instructions for treatment very carefully.

© 1966 AYERST LABORATORIES
Division of American Home Products Corporation

A WORD ABOUT SKIN INFECTIONS

There are many different types of skin infections. Some, such as "boils," are caused by bacteria. Others, such as "warts," may be produced by a virus. Still others are produced by fungi, especially of the ringworm type.

Fungus infections are nothing new under the sun. They have probably plagued man, his domestic animals, and his crop plants from the beginning of time. Today, they number among the most common skin infections. Some are found only in the tropics. Or mainly on the Asian or European continents. Others may be seen anywhere in the world.

At this point, it may be a good idea to add a thought or two about your skin. It's tough and pliable. But it's only as good or as bad as your general health can make it. It provides a remarkable protective "wrapping" for body organs and tissues, and is practically germ proof when the skin is unbroken.

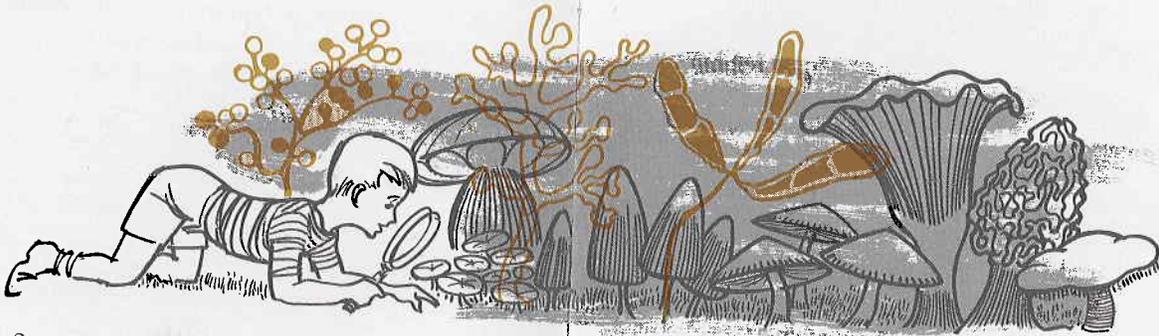
FASCINATING AND FRUSTRATING FUNGI

If all known fungi were collected into one gigantic box and opened by a curious Pandora, more than 75,000 species would come tumbling out. Yeasts and molds, rusts and smuts, mildews and dry rots, blights and mushrooms. As small as 1/250,000 of an inch across! As big as a foot across and weighing 20 pounds! Each one a fascinating specimen. Some weird of shape. Others exotically colorful.

Fungi are not at all like your favorite greenhouse plant. They have no roots, stems or leaves. Containing no chlorophyll, they cannot convert the sun's energy to food. So they become scavengers and parasites. Often, they are nature's most notorious destroyers, frustrating man in his efforts to control the damage they cause.

On the other hand, fungi may provide untold blessings. You probably know that yeasts are used in baking and brewing. Some molds are useful in making chemical acids, vinegar or cheese. Then, there is the famous mold that has given us the lifesaving antibiotic, penicillin.

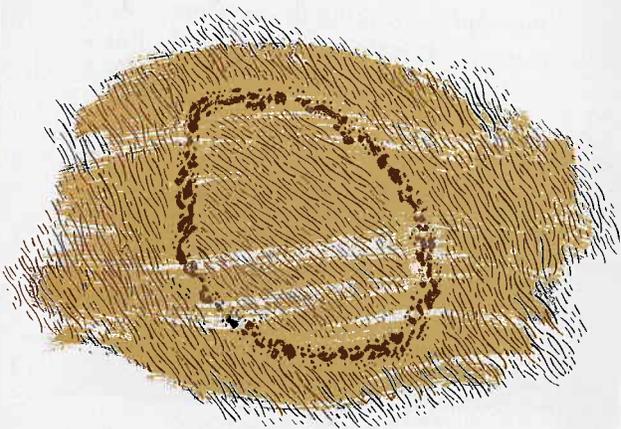
Actually, only a handful of about 50 of the sprawling fungi family cause disease in man or animals. Broadly speaking, fungi may be divided into two groups: *zoophilic* and *anthropophilic*. Zoophilic fungi infect animals and may be transmitted to man. Anthropophilic fungi are those that infect man and are only rarely transmitted to animals.



RINGWORM—WHAT'S IN A NAME?

Certainly seems an odd way to identify an infection of the skin. It's not caused by a worm, as we know, but by a fungus. There must be a reason. Look closely at the illustration shown on this page. Notice how the affected area has a ring-shaped, scaly appearance. Ringworm often spreads in this manner. So, perhaps, its name is not so strange after all.

By any name, the fact is that ringworm fungi are the most important of the superficial fungi. They are classified into three main groups bearing Greek-derived, tongue-tripping names — *Microsporum*,



Trichophyton, and *Epidermophyton*. These three mother groups have fostered about 15 to 20 fungal offspring, common causes of superficial fungus (ringworm) infections of the hair and scalp, nails, and skin.

There's a technical name for ringworm infections. It's called *tinea*, and is usually enlarged upon to include the part of the body affected. For instance, *tinea capitis* or ringworm of the scalp. *Tinea pedis* or ringworm of the feet. *Tinea unguium* or ringworm of the nails, to mention a few.

Before we go on, let's clarify the meaning of "superficial." It simply means that the infection is confined to the outer (top) layer of the skin.

Now, remember how we described fungi—as plant life that cannot feed itself. What, then, do ringworm fungi do for nourishment? Apparently, they have a gourmet-like appetite for "keratin"—for "nonliving" rather than living tissue.

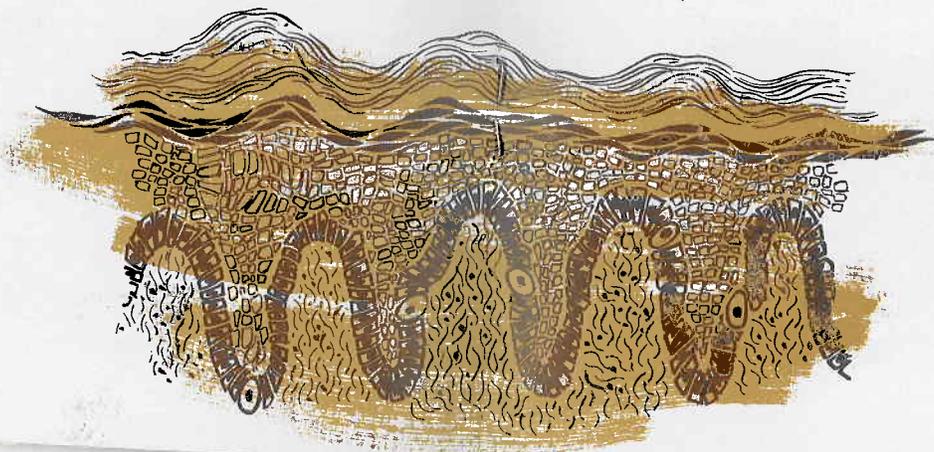
A TOUGH PROTECTOR— KERATIN

Keratin is the building stuff of hair, nails, and the outermost layer of the skin. It is often called the “horny” layer. This outer skin layer is dead, made up entirely of keratinized cells. The keratin structure is a tough fibrous protein. It protects the thin, top layer of the skin pretty much the way bark does a tree.

How, if this is so, do ringworm fungi get past this barrier? They contain an enzyme—a keratin solvent that can digest and break down keratin. When keratin is attacked in this way, the hair can dissolve and split. It could cause baldness. Nail growth can be completely altered. And the structure of the entire horny layer may be thrown into disorder.

What is the counterattack against invasion by ringworm fungi? The answer did not come easily. Keratin, as was soon realized, resisted ordinary topical (applied to the surface) remedies in the same way it warded off external injury. Most antifungal ointments, creams, powders, and solutions simply cannot penetrate the skin deeply enough to get at the fungus infection.

If you recall the fable, after Pandora opened the box and allowed all the human ills to escape, she replaced the lid. One thing still lay at the bottom of the box—*hope*. Surely, this must be a quality that research scientists have in reserve. For, when it was found that it wasn't possible to get around the problem of ringworm fungi from the outside, they started to think about treatment from the inside of the body.

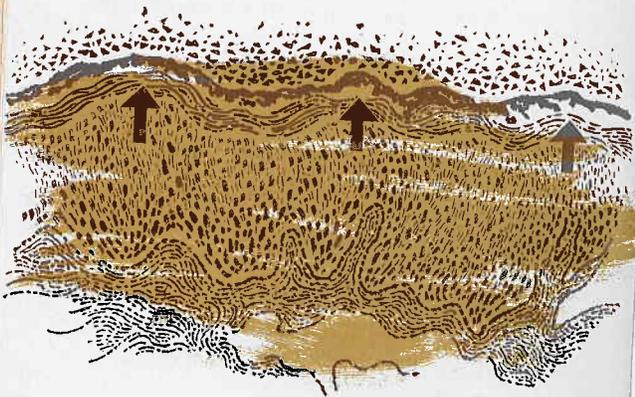


A BIG STEP FORWARD— GRISEOFULVIN

Eventually, the pieces in the medical puzzle were put together. An antifungal agent, griseofulvin, first studied for possible value in attacking fungus infections in plants, was later found to be useful in combatting fungus infections in man.

It might be said that griseofulvin meets the ringworm fungus on its own ground. After an oral dose, griseofulvin is taken into the body by the stomach. Then, it's picked up by the blood which carries it to the skin, hair, and nails.

Griseofulvin does not actually go into the horny layer and attack the ringworm fungi. Rather, it becomes a part of the



new keratin growth. This acts as a barrier to the fungi and gives the natural processes of body repair a chance to take over. Then, as the new keratinized cells move toward the surface, the dead cells are shed. The fungi are carried out with them, and are replaced by new, healthy skin, hair, and nails harboring no fungi.

Why is griseofulvin considered such an important step forward in the treatment of superficial fungus infections? Because it is effective and convenient treatment. Because it has proved highly active against all known species of *Microsporum*, *Trichophyton*, and *Epidermophyton*. Because, in reducing the time needed for treatment, it may actually be less expensive than older methods of treatment.

Griseofulvin has become a reliable treatment for superficial fungus (ringworm) infections. But, when you're taking griseofulvin, don't become impatient. Even this drug cannot take full effect until infected skin, hair, or nails have been "pushed out" and replaced with the new.

It's also true that results depend upon the type of fungus being treated. Ringworm of smooth, nonhairy skin, for example, may take two to four weeks. Probably three to five weeks are needed for ringworm of the scalp. Ringworm of the nails is most difficult of all. Three to six months for fingernails. At least eight to twelve months for toenails.

Of course, these are all average figures that vary greatly with different individuals. Sometimes less time is needed. Often, treatment may take much longer.

Obviously, it is important to obtain adequate treatment. Even when the infection seems cleared up, the fungus may still be alive. Griseofulvin stops the growth of ringworm fungi. It does not kill them. For this reason, you should take medication as long as your doctor believes necessary.

TO SUM UP:

With the foregoing in mind, you will no doubt agree that treatment of your fungus infections is a two-way effort. Your doctor will prescribe the medication as well as any special procedures that are indicated. You must then cooperate fully by following his instructions carefully and faithfully. Above all, be sure to continue treatment under your doctor's supervision for the full period of time that he recommends.

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29				



*This booklet is supplied
with the compliments of
AYERST LABORATORIES
New York, N.Y. 10017*

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BO168-144-570

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0168



Ayerst[®]

GRISACTIN[®]

BRAND OF

**GRISEOFULVIN
(MICROSIZE)**

CAUTION: Federal law prohibits dispensing without prescription.

GRISACTIN [griseofulvin (microsize)] is produced by a special process that fractures particles into minute crystals of irregular shape offering a greater and more effective surface area for increased gastrointestinal absorption.

This enhanced absorption is reflected in higher serum levels, and therefore half the dosage is sufficient to produce the same therapeutic effect as that of a full dose of regular griseofulvin. Blood level studies carried out in normal fasting male subjects clearly demonstrated an increased intestinal absorption of GRISACTIN. The same order of serum levels resulted from a single dose of 0.5 Gm. of GRISACTIN as from a single dose of 1.0 Gm. of regular griseofulvin. Other blood level studies indicate that with either tablets or capsules, absorption of griseofulvin (microsize) is compar-

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79

able when given in equal amounts as a single dose.

GRISACTIN [griseofulvin (microsize)] has a potent fungistatic action, particularly against those fungi responsible for dermatomycoses in man and animals, namely:

Microsporium canis
M. gypseum
M. audouini
Epidermophyton floccosum
Trichophyton tonsurans
T. rubrum
T. mentagrophytes
T. megnini
T. gallinae
T. verrucosum
T. sulfureum
T. interdigitale
T. schoenleinii
T. crateriform

This preparation is not active against:

Candida albicans (monilia)
Cryptococcus neoformans
Blastomyces dermatitidis
Actinomyces israeli
Histoplasma capsulatum
Coccidioides immitis
Malassezia furfur (tinea versicolor) and bacteria

INDICATIONS

Recommended 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)

Prior to the institution of therapy, the type of fungi responsible for the infection should be identified by culture.

CONTRAINDICATIONS

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin. The use of this drug is not justified in minor or trivial infections which will respond to topical antifungal agents alone.

PRECAUTIONS

As with all antibiotics, the use of this drug may result in an overgrowth of nonsusceptible organisms, particularly monilia. Continuing observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken.

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic, and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross-sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Safety of this drug for use in pregnancy has not yet been established.

SIDE EFFECTS

Serious side effects reported with griseofulvin therapy are rare and are usually associated with high dosages and/or long periods of therapy.

Reactions are 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 rarely been reported 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; photosensitivity (patients should be warned to avoid exposure to intense natural or artificial sunlight).

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

ADMINISTRATION AND USUAL DOSAGE

The amount, frequency, and duration of administration are variable, depending on the age of the patient, severity of the infection and practicality of the regimen.

Adults: 0.5 Gm. daily (125 mg. q.i.d., 250 mg. b.i.d., or 500 mg./day). Patients with less severe or extensive infections may require less, whereas those with widespread lesions may require a starting dose of 0.75 Gm. to 1.0 Gm. a day. This may be reduced gradually to 0.5 Gm. or less after a response has been noted. In all cases, the dosage should be individualized.

Children: A dosage of 10 mg./Kg. daily is usually adequate (children from 30 to 50 lb., 125 mg. to 250 mg. daily; children over 50 lb., 250 mg. to 500 mg.

in divided doses). Dos-
should also be individual-
as with adults.

GENERAL ADJUNCTIVE MEASURES

der to prevent reinfection
ence a recurrence of the
s disease, general hygienic
ures should be maintained.
iliness is of major impor-
All wearing apparel, hats,
ear, pillows, and certain
estic animals are likely to
ources of infection. In pa-
s with tinea capitis, tinea
ae, or tinea unguium, clip-
of infected portion of hair
ail should be done to reduce
bility of reinfection.

AVAILABILITY

GRISACTIN [griseofulvin (micro-
)]

3442—Each capsule con-
s 125 mg., in bottles of 100
500.

3443—Each capsule con-
s 250 mg., in bottles of 100
500.

3444—Each tablet (scored)
contains 500 mg., in bottles of

AYERST LABORATORIES
INCORPORATED
New York, N.Y. 10017

Available by arrangement with
IMPERIAL CHEMICAL INDUSTRIES
LIMITED

Revised December 1968.

PRINTED
IN
U.S.A.

Contains 12 Patient Booklets—
"Some Facts on Fungal Skin Infections"

CAUTION: Federal law prohibits
dispensing without prescription.

This dispenser contains 12 units
of 2 tablets each. Each tablet
(scored) contains 500 mg. griseo-
fulvin (microsize).

Usual dosage: Adults, 0.5 Gm.
daily. Children, 10 mg./Kg. daily.

See enclosed package circular for
complete prescribing information.

444 Control No. 2ADV
Exp. Date Jan. '74

Ayerst®

AYERST LABORATORIES INCORPORATED
New York, N.Y. 10017

GRISACTIN® [griseofulvin (microsize)] is available in the United States
by arrangement with Imperial Chemical Industries Ltd.

Issued February 1970.
B0167-12-570

Printed in U.S.A.

0167

Grisactin[®] 500

Brand of

GRISEOFULVIN (MICROSIZED)

Tablets

444 Control No. 2ADV
Exp. Date Jan. '74

Ayerst[®]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 60-212

CHEMISTRY REVIEW

OCS REVIEW NOTES
FORM 6

50-051

Ayerst Laboratories
685 Third Avenue
New York, N.Y.

60-212

1. 50-051 Griseactin (griseofulvin microsize) capsules
60-212 Griseactin (griseofulvin microsize) tablets

Human use
Oral administration

2. Components & Composition

(b) (4) griseofulvin is made by (b) (4)
(b) (4) Ayerst has the (b) (4) griseofulvin (b) (4) by
either (b) (4)

<u>Active Ingredient</u>	<u>Tablet</u>	<u>Capsule</u>	<u>Capsule</u>
Griseofulvin microsize	500 mg	125 mg	250 mg

Inert Ingredients

(b) (4)
mg
mg

3. Raw Material Controls

1. The Form 6 does not correlate the batches of (b) (4) griseofulvin received from (b) (4) to the batches of microsize griseofulvin submitted to the FDA for testing.

2. The (b) (4) and (b) (4) and (b) (4) conform to U.S.P. specifications. The firm runs an identity on the (b) (4) and the (b) (4).

3. The microsize griseofulvin is tested according to the monograph.

4. Manufacturing, Processing and Packaging procedures

- a. The firm has adequate equipment for the manufacturing and packaging of the drug.
- b. The Form 6 does not give any details concerning in-process controls.
- c. Final Product controls are adequate.
- d. Sample collection is adequately defined in the Form 6.

5. Laboratory Facilities for control tests

- a. The firm has two quality control laboratories, a laboratory located at Housatonic Point, N.Y., and a laboratory in Montreal, Canada.
- b. The laboratory facilities are adequate.
- c. The tests on the raw material and finished product are adequate, however, the Form 6 does not specify which of two monograph potency tests is used by the firm.

6. Stability data:

The stability data submitted in the Form 6 does not give adequate information concerning the conditions under which the material is stored.

7. Batch Identification Procedures:

The significance of the batch numbering system is adequately explained in the Form 6.

8. Labeling

The labeling is adequate.

9. The last general inspection was made under IDIP which was terminated in late 1970. The firm was found to be operating under satisfactory GMP's.

Comments:

The Form 6 is considered incomplete for the following reasons:

1. The Form 6 does not correlate the batches of (b)(4) griseofulvin received from (b)(4) to the batches of microsize griseofulvin submitted to FDA for testing.
2. The exact method of potency assay used by Ayerst on the microsize griseofulvin and the griseofulvin capsules and tablets should be stated in the Form 6.
3. Since the firm has two quality control laboratories, the functions of each regarding griseofulvin should be defined in the Form 6.
4. The firm did not include a description of the in-process controls, or the methods and processes used in the manufacture of the drugs.
5. Stability studies should be expanded to include type drug container, also light and humidity storage conditions.

William E. Megner
Certifiable Drug Review Staff
Division of Anti-Infective Drug
Products

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 60-212

MICROBIOLOGY REVIEWS

Form 6

January 29, 1969

MICROBIOLOGIST'S SUMMARY OF FORM 6
Original Summary

Sponsor: Ayerst Laboratories
New York, New York

Product: Grisactin, Griseofulvin, microsize, Tablets, 500 mg.

Form 6 OCS Document No. 60-212

1. This dosage form has been previously approved for use by the Department of Defense. The blood level data in the submission were performed in September, 1967, before the requirement for these studies in an IND was in effect.
2. The blood level data consist of a single crossover experiment in 16 normal male volunteers comparing a single 500 mg. tablet with two 250 mg. capsules of the presently marketed formulation. Serum levels were determined by a chemical method. Examination of the data show that the levels obtained with the tablet are slightly lower than those obtained with the two capsules, but both are well within the concentration range obtained with similar dosages in the scientific literature.
3. I recommend approval of this application.


William E. Dye, Ph.D.

cc:
Dup Form 6 (OCS/CC-100)
OCS/OD/CC-100
OND/MD-100
DAD/MD-140
WEDye/MD-140/cw
Typed 1-30-69
R/D initialed by AESmith 1-29-69

 1/31/69

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 60-212

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Pharmaceuticals Through Medical Research

Ayerst
®

685 Third Avenue, New York, N. Y. 10017 • (212) YUKon 6-1000 / Cable: ALPHAMIN, New York

December 6, 1967

Dr. Daniel Banes
Acting Director
Division of Antibiotics and Insulin Certification
Bureau of Science (S-100)
Food and Drug Administration
Washington, D. C. 20204

Dear Dr. Banes:

Subject: GRISACTIN® [griseofulvin (microsize)] Tablets.

We are transmitting herewith in triplicate, as required under Section 146.2 of the regulations for the certification of antibiotics, an Antibiotic Form FD-1675 to provide for the marketing of Grisactin [griseofulvin (microsize)] in tablets each containing 500 mg. of the antibiotic.

We have been marketing Grisactin [griseofulvin (microsize)] Capsules, 125 mg. and 250 mg., under an approved NDA 13-236 and Griseofulvin (large particle) Tablets, 250 mg. and 500 mg., under an approved NDA 12-156 for several years. The Administration has been approving batches of such capsules and tablets on a "release" basis, pending finalization of the regulations which will cover the several griseofulvin dosage forms. We should like to have the 500 mg. griseofulvin (microsize) tablet approved, also on a "release" basis, and included in the regulation for Grisactin Tablets when it is finalized.

Draft copies of the labeling we plan to use for Grisactin Tablets are included in Part 6 of this submission. We should like to note that we presently plan to market the Grisactin Tablets on a contract basis only with the Federal Government's Defense Supply Agency. Thus, the content of the label and carton copy included herein is in accordance with the requirements set forth by the DSA. The package insert which will be used is essentially the same as currently approved for our Grisactin Capsules. Editorial adjustments have been limited to deleting reference to the capsule dosage form. No changes are proposed in the indications for use or in the suggested total daily dose of this product.

10598

(continued . . .)

AYERST LABORATORIES

Dr. Daniel Banes

-2-

December 6, 1967

Exhibit samples will be sent to the Administration under a separate covering letter from our facilities at Rouses Point, New York. We should like to proceed promptly with the preparation of materials prerequisite to final approval for the product, and we will sincerely appreciate your consideration of this information at your early convenience.

Sincerely,

AYERST LABORATORIES

Howard E. Cmejla
per [signature]

Howard E. Cmejla, Ph. D.
Director, Regulatory Liaison

HEC:mt
Encs.
RLH

ANTIBIOTIC APPLICATION

(Check applicable item below)		FOR USE OF FOOD AND DRUG ADMINISTRATION	
FORM 5 REQUEST UNDER 146.10 TO PROVIDE FOR CERTIFICATION OF A NEW ANTIBIOTIC OR ANTIBIOTIC-CONTAINING PRODUCT.	<input type="checkbox"/>	DATE APPROVED	ACCOUNT NO.
FORM 6 DATA TO ACCOMPANY OR PRECEDE EVERY INITIAL REQUEST UNDER 146.2 FOR CERTIFICATION OF AN ANTIBIOTIC DRUG COVERED BY EXISTING REGULATIONS.	<input checked="" type="checkbox"/>	SIGNED	
SECTION _____			
FORM 5 AMENDMENT. REGULATION SECTION _____ IF KNOWN.	<input type="checkbox"/>	FOR THE COMMISSIONER OF FOOD AND DRUGS FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE	
FORM 6 AMENDMENT. REGULATION SECTION _____	<input type="checkbox"/>		
NAME OF APPLICANT		DATE OF APPLICATION	
AYERST LABORATORIES			
ADDRESS (Include Zip Code)			
685 Third Avenue, New York, New York 10017		December 12, 1967	
NAME OF DRUG			
GRISACTIN® [griseofulvin (microsize)] TABLETS, 500 mg.			

Commissioner
 Food and Drug Administration
 Department of Health, Education, and Welfare
 Washington, D.C. 20204

Attention: Division of Antibiotics and Insulin Certification

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 milliliter, 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.

- (b) 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 (c).
- (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.

- (b) 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 in the container including a multiple-dose container in which it is to 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 any 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 to 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 1.106(b) or (c).
- (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 informa-

tion 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 provisions of §130.3.
- (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

Howard E. Cmejla,
Director, Regulatory Liaison

(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 Division of Antibiotics and Insulin Certification 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 for 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.

AF 19-003

January 15, 1968

Dr. Howard E. Guejla
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Guejla:

Reference is made to your letter of December 6, 1967,
with which you submitted a Form 6 for griseofulvin
(microsize) tablets, 500 mg. (Grisactin).

The information and labeling are satisfactory.

You may submit samples for testing with a view to
batch release of this drug.

Sincerely yours,

Paul E. Ogles
Assistant to the Director
Division of Antibiotics and
Insulin Certification
Bureau of Science

cc:
NYK-DO
S-100
S-100/OD
S-100/Lab
PEOgles:jh

Ayerst[®]

685 Third Avenue, New York, N. Y. 10017 • (212) YUKon 6-1000 / Cable: ALPHAMIN, New York

May 20, 1968

Dr. William W. Wright
Acting Deputy Director
Division of Pharmaceutical Sciences
Bureau of Science
Food and Drug Administration
Washington, D. C. 20204

Dear Dr. Wright:

Subject: GRISACTIN[®] / griseofulvin (microsize) Tablets, 500 mg.

We are transmitting herewith, in triplicate, amendments to Parts 1, 2, 3(c), and 3(i) of our Antibiotic Form FD-1675 for this product to provide for a revision in the formula of the tablets. The revised formula is identical to that given in our Form FD-1675 which was approved on February 13, 1968, except that the amount of (b)(4) in the tablet is reduced and (b)(4) is added at a level not to exceed (b)(4)% of the total tablet weight. This change in formulation improves the tablet disintegration rate and allows us to meet the current D.S.A. specification.

We should appreciate the Administration's early consideration and approval of this manufacturing change.

Sincerely,

AYERST LABORATORIES

Howard E. Cmejla
per [signature]
Howard E. Cmejla, Ph. D.
Director, Regulatory Liaison

HEC/mdb
RLH
Enc.

13240

AF 19-003

May 27, 1968

Howard E. Caejla, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Caejla:

This is to acknowledge receipt of the Form 6 amendment submitted May 20, 1968, to provide for the inclusion of (b) (4) in your formula for GRISACTIN (griseofulvin, microsize) Tablets, 500 mg. The revision in the formulation appears acceptable and the information presented will be added to your pending Antibiotic Form 6 application for this drug.

A signed copy of the Form 6 application will be returned to you when the final regulations to provide for the certification of griseofulvin are published in the FEDERAL REGISTER.

Sincerely yours,

John D. Harrison
Office of Certification
Services

cc: NYK-DO
CC-100
CC-100 (reading file)

JDHarrison: jk

AYERST LABORATORIES *Pharmaceuticals Through Medical Research*
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Ayerst
®

685 Third Avenue, New York, N. Y. 10017 • (212) YUKon 6-1000 / Cable: ALPHAMIN, New York

October 2, 1968

Mr. Robert C. Brandenburg
Director,
Office of Certification Services
Food and Drug Administration
Washington, D.C. 20204

Dear Mr. Brandenburg:

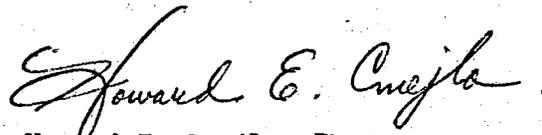
Subject: GRISACTIN[®] (griseofulvin microsize) Tablets.

We wish to advise the Administration that earlier this year we instituted a revised procedure of assigning batch numbers and control numbers. We are enclosing herewith, in triplicate, copies of this revised procedure. We are also enclosing copies of the product distribution control procedure.

We should like this information to be included in the Administration's files for Grisactin Tablets.

Sincerely,

AYERST LABORATORIES



Howard E. Cmejla, Ph.D.
Director,
Regulatory Liaison

HEC/kjm
MNF
Encls.

October 11, 1968

Howard E. Cmejla, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Cmejla:

This is to acknowledge receipt of your submission of October 2, 1968, to provide for a description of your revised batch numbering system in the Form 6 for GRISACTIN (griseofulvin microsize) TABLETS. The new numbering system is acceptable and the description will be added to the Form 6 file for this product.

Sincerely yours,

John D. Harrison
Office of Certification
Services

cc: NYK-DQ
CC-100
CC-100 O/D

JDHarrison: jk

AYERST LABORATORIES *Pharmaceuticals Through Medical Research*
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Ayerst®

685 Third Avenue, New York, N. Y. 10017 • (212) YUkon 6-1000 / Cable: ALPHAMIN, New York

November 7, 1968

Mr. Robert C. Brandenburg
Director
Office of Certification Services
Food and Drug Administration
Washington, D. C. 20204

Dear Mr. Brandenburg:

Subject: Griseofulvin (regular size) Tablets, 250 mg. and 500 mg.

Our NDA 12-156 for Griseofulvin Tablets currently states that the moisture content of the finished tablets shall be not more than $\frac{(b)}{(4)}\%$. Extensive manufacturing experience shows that this specification can be met but, on occasion, the tablet

(b) (4)
the tablets. In order to improve our manufacturing operations, we propose to change the moisture limit to conform to the Administration's regulations for Griseofulvin Tablets proposed in the January 19, 1966 Federal Register, wherein the specification is stated as follows, "The moisture content is not more than 5%".

16065 ✓

Since we should like to effect this change as soon as possible, we will sincerely appreciate your consideration of this proposal at your earliest convenience.

Sincerely,

AYERST LABORATORIES

Howard E. Cmejla

Howard E. Cmejla, Ph. D.
Director, Regulatory Liaison

HEC:gjf

November 20, 1968

Howard E. Gmejia, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Gmejia:

This is to acknowledge receipt of the amendment submitted November 7, 1968, to provide for a maximum moisture limit of 5% in your Griseofulvin (regular size) Tablets, 250 mg., and 500 mg. We have no objection to this new specification.

Sincerely yours,

John D. Harrison
Office of Certification
Services

cc:

CC-100
CC-100/OD
SC-840/Lab

JDHarrison:dc

AYERST LABORATORIES *Pharmaceuticals Through Medical Research*
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Ayerst[®]

685 Third Avenue, New York, N. Y. 10017 • (212) YUKon 6-1000 / Cable: ALPHAMIN, New York

November 25, 1968

Mr. Robert C. Brandenburg
Director
Office of Certification Services
Food and Drug Administration
Washington, D. C. 20204

Dear Mr. Brandenburg:

Subject: GRISACTIN[®] [griseofulvin (microsize)] Tablets, 500 mg.

On December 6, 1967 we submitted a Form 6 to provide for the availability of this product to be distributed on a contract basis with the Federal Government's Defense Supply Agency. The proposal was approved on January 15, 1968 and final printed labeling was approved on February 13. As discussed recently with Mr. John D. Harrison, we now plan to market this product through our usual channels of commercial distribution.

In order to prepare for testing with a view to batch release of this product, we are transmitting herewith, in draft form, copies of the label, carton, package insert, and brochure we plan to utilize. The carton will be a window type permitting full view of the main panel of the label which has been noted in the attached copy. Our current package insert for Grisactin has been adjusted editorially in only minor respects. The brochure which was approved on November 2, 1965, but which has not been used during the past several years, has been revised: (1) to up-date the copy to conform with the approved package insert, and (2) to incorporate a summary of the blood level studies which were reported in detail in our submission of December 6, 1967.

16286

We are also transmitting herewith amendments to Parts (1), (2), (3)(c), and (3)(i) to provide for an alternative formulation of tablets which will include a dye. This alternative formulation will apply in the manufacture of batches which we plan to market through our usual channels of distribution.

(Continued . . . 2)

Mr. Robert C. Brandenburg

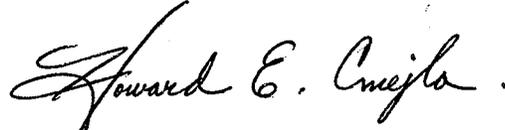
-2-

November 25,

We will look forward to consideration and approval of these proposals at your earliest convenience.

Sincerely,

AYERST LABORATORIES

A handwritten signature in cursive script that reads "Howard E. Cmejla".

Howard E. Cmejla, Ph. D.
Director, Regulatory Liaison

HEC:gjf

Encs.

December 16, 1968

In reply refer to:
#60-212 - 148g.2

Howard E. Cnefja, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Cnefja:

This is to acknowledge receipt of the amendment submitted on November 23, 1968, to your pending Form 6 application for Griseofulvin (griseofulvin microsize) Tablets, 500 mg. The amendment consisted of a revised formulation, required labeling and promotional labeling for bottles of 60 tablets.

This submission has been forwarded to the Bureau of Medicine - Division of Anti-infective Drugs for medical evaluation. You will be informed when the review is completed.

Sincerely yours,

I. David Powers
Food and Drug Officer
Office of Certification Services

cc:
CG-100
CG-100/OD
Dr. Alan Smith, MD-140
SG-840/Lab }
IDPowers:jh

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 12/16/68
FROM: J. David Powers CC-100		OFFICE OND
TO: Dr. Alan Smith MD-140		DIVISION DAD
SUBJECT: Urgent amendment to their pending Form 6 for		
<small>SUMMARY</small> Grisactin (griseofulvin microsize) Tablets, 500 mg (11/6/68)		
Please review the attached submission with special emphasis on:		
<ol style="list-style-type: none"> 1. The "pharmacological category" on the label. This is not required on <u>prescription</u> labeling. 2. The proposed new sentence on the first page of the package insert. 3. The proposed "Professional Brochure" 		
I am attaching the latest package inserts we have plus blood level studies submitted on Dec. 6, 1967. We have no indication in the files that these studies were reviewed by a medical officer and/or a pharmacologist.		
Please return to me with your comments.		
SIGNATURE J. David Powers	DOCUMENT NUMBER 60-212	

Form 6

January 20, 1969

Memorandum of Telephone Conversation

Between: Howard E. Cmejla, Ph. D.
Ayerst Laboratories
New York, New York

and

William E. Dye, Ph. D.
Division of Anti-infective Drugs
Office of New Drugs



Dr. Cmejla called at 9:30 a.m. to inquire about the status of an amendment to their Form 6 for Grisactin Tablets, 500 mg. submitted November 25, 1968.

I told Dr. Cmejla that I had reviewed the blood level data in the application and that I believed it was satisfactory for approval by this Division. I also told him it was subject to further review by the Office of the Director of the Bureau of Medicine and that I could not estimate the period of time which might be required for clearance after it left this office.

I also told him that I had asked Mr. Norton to look over some reprints on correlation of dissolution rates with the "bio-availability" of this drug and to consider whether dissolution rate data should be part of the quality control procedures.

I also told him that I understood that labeling changes were also being made on the basis of the NAS/NRC review and that this might further delay action on this application.

cc:

~~OCS/CC-100 EB-8~~

OCS/CC-100

OCS/CC-100/OD

OND/MD-100

DAD/MD-140

Med/MD-14

WEDye/MD-140/vew

Typed: 1/22/69

R/D Init: AESmith 1/21/69

noted
Alan J Smith 1/22/69

William E Dye
William E. Dye, Ph. D.

UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE
Food and Drug Administration

Memorandum

TO : Mr. Robert C. Brandenburg
Office of Certification Services (CC-100)

DATE: January 30, 1969

FROM : B. H. Minchew, M.D., Acting Director
Bureau of Medicine (MD-1)

Ayerst Labs.
New York, N.Y.
Form 6

SUBJECT: Amendment to Form 6 application for Griseofulvin
microsize, Ayerst Laboratories

It is recommended that this amendment to the above named application to include a 500 mg. size tablet be approved.

The same size tablet has been approved for military use. This application includes labeling for civilian use. The draft copy of such labeling has been approved.

If additional information relating to the safety and efficacy of this drug, including a report of the evaluation of the drug by the National Academy of Sciences-National Research Council, becomes available, revision of the labeling may be required.


B. H. Minchew, M.D.

cc:
Orig Form 6 (OCS/CC-100)
Dup Form 6 (OCS/CC-100)
OCS/OD/CC-100
Med/MD-1
OND/MD-100
DAD/MD-140
Med/MD-14



UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE
Food and Drug Administration

Memorandum

TO : B. H. Minchew, M.D., Acting Director
Bureau of Medicine (MD-1)

B.H. Minchew
2/13/69

DATE: January 30, 1969
Through:
William J. Gyarfas, M.D.
Acting Director (MD-101)

FROM : Alan E. Smith, M.D., Deputy Director
Division of Anti-infective Drugs (MD-140)

Alan E. Smith

SUBJECT: Griseofulvin microsize 500 mg. tablets

Ayerst Labs.
New York, N.Y.
Form 6

This application is an amendment to the Form 6 application to include a 500 mg. size tablet for civilian use. The same size tablet has previously been approved for use by the military.

The blood level data has been reviewed by this Division and has been termed acceptable.

The labeling has been revised to indicate the new dosage size and administration.

It is recommended that this application be approved.

The firm is aware of the fact that revision of the label may be required when the NAS-NRC panel reports have been implemented.

Alan E. Smith
Alan E. Smith, M.D.

cc:
Orig Form 6 (OCS/CC-100)
Dup Form 6 (OCS/CC-100)
OCS/CC-100/OD
Med/MD-1
OND/MD-100
DAD/MD-140
Med/MD-14

P.S.
The "other blood level studies" referred to in the opening section of the package insert were included in the application for "military use" and were approved in labeling for such as of February 13, 1968. They were reported in Part 9, report 67-11 in the submission of December 6, 1967.

Alan E. Smith



MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 2/13/69
FROM: Act. Dir -		OFFICE
TO: OND - Mrs Hyarjus / A. Smith		DIVISION
SUBJECT: Form 6 Anisopulvin microsize - Syerst		
<p>SUMMARY</p> <p>Before approving I need clarification on 1 point. Dr. Dye's Jan 29, 1969, summary states that the blood level studies were performed "in Sept. 1967, before the requirement for an IND was in effect"? IND requirements went into effect June, 1963 - what am I missing?</p> <p>Three words "these studies in" have been added to the first paragraph of Dr. Dye's summary.</p> <p style="text-align: right;">A. Smith 2/14/69</p> <p>wjg 2/14/69</p> <p>Signed 2/18/69 B.H. Minchew</p>		
SIGNATURE B.H. Minchew	DOCUMENT NUMBER	

RECEIVED

FEB 18 1969

OFFICE OF NEW DRUGS
- BUREAU OF MEDICINE
FOOD AND DRUG ADMINISTRATION, DHEW

NOTE.—DO NOT USE THIS ROUTE SLIP TO
SHOW FORMAL CLEARANCES OR APPROVALS

DATE

TO:

AGENCY BLDG. ROOM

Dr. Munchew

- | | | |
|---|--|---|
| <input type="checkbox"/> APPROVAL | <input type="checkbox"/> REVIEW | <input type="checkbox"/> PER CONVERSATION |
| <input type="checkbox"/> SIGNATURE | <input type="checkbox"/> NOTE AND SEE ME | <input type="checkbox"/> AS REQUESTED |
| <input type="checkbox"/> COMMENT | <input type="checkbox"/> NOTE AND RETURN | <input type="checkbox"/> NECESSARY ACTION |
| <input type="checkbox"/> FOR YOUR INFORMATION | | |
| <input type="checkbox"/> PREPARE REPLY FOR SIGNATURE OF _____ | | |

REMARKS:

*appears to be in order - NO
summaries but action is apparently
based on previous approval for
military use*

(Fold here for return)

To

From

PHONE

BUILDING

ROOM

R E Newberry 2/2/69

FORM HEW-30 REV. 11/56

ROUTE SLIP

GPO: 1956-O-409606

PUBLIC HEALTH SERVICE

In reply refer to 148g.2

February 24, 1969

Howard E. Cmejla, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Cmejla:

The amendment submitted on November 25, 1968, to your pending Form 6 application for Grisactin (griseofulvin microsize) Tablets, 500 mg. for non-military use to be packaged in bottles of 60 tablets has been reviewed by the Bureau of Medicine and found to be satisfactory.

Please submit three specimens of each piece of labeling involved in the amendment, in final printed form, for approval. When this is received, we can give further consideration to releasing batches of these tablets submitted for testing.

Sincerely yours,

I. David Powers
Office of Certification
Services

cc: CC-100
CC-100 O/D

IDPowers: jk



685 Third Avenue, New York, N. Y. 10017 • (212) YUKon 6-1000 / Cable: ALPHAMIN, New York

March 6, 1969

Mr. I. David Powers
Office of Certification Services
Food and Drug Administration
Washington, D. C. 20204

Dear Mr. Powers:

Subject: NDA 60-212, GRISACTIN® [*griseofulvin (microsize)*] Tablets, 500 mg.

Thank you for your letter of February 27, 1969 approving the final printed labeling for this product. We are transmitting herewith copies of a revised printed package insert in which we have corrected an editorial inconsistency in the section titled "Administration and Usual Dosage". The wording, "Adults: 0.5 Gm. daily (125 mg. q.i.d. or 250 mg. b.i.d.)", should have read, "Adults: 0.5 Gm. daily (125 mg. q.i.d., 250 mg. b.i.d., or 500 mg./day).

Sincerely,

AYERST LABORATORIES

A handwritten signature in cursive script that reads "Howard E. Cmejla".

Howard E. Cmejla, Ph. D.
Director, Regulatory Liaison

HEC:gjf
Encs.

daily, in divided doses). Dosage should also be individualized, as with adults.

GENERAL ADJUNCTIVE MEASURES

In order to prevent reinfection and hence a recurrence of the fungus disease, general hygienic measures should be maintained. Cleanliness is of major importance. All wearing apparel, hats, footwear, pillows, and certain domestic animals are likely to be sources of infection. In patients with tinea capitis, tinea barbae, or tinea unguium, clipping of infected portion of hair or nail should be done to reduce possibility of reinfection.

AVAILABILITY

GRISACTIN [griseofulvin (micro-size)]

No. 3442—Each capsule contains 125 mg., in bottles of 100 and 500.

No. 3443—Each capsule contains 250 mg., in bottles of 100 and 500.

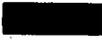
No. 444—Each tablet (scored) contains 500 mg., in bottles of 60.

AYERST LABORATORIES
INCORPORATED
New York, N.Y. 10017

Available by arrangement with
IMPERIAL CHEMICAL INDUSTRIES
LIMITED

Revised December 1968.

PRINTED
IN
U.S.A.


Ayerst®

GRISACTIN®

BRAND OF

**GRISEOFULVIN
(MICROSIZED)**

CAUTION: Federal law prohibits dispensing without prescription.

GRISACTIN [griseofulvin (micro-size)] is produced by a special process that fractures particles into minute crystals of irregular shape offering a greater and more effective surface area for increased gastrointestinal absorption.

This enhanced absorption is reflected in higher serum levels, and therefore half the dosage is sufficient to produce the same therapeutic effect as that of a full dose of regular griseofulvin. Blood level studies carried out in normal fasting male subjects clearly demonstrated an increased intestinal absorption of GRISACTIN. The same order of serum levels resulted from a single dose of 0.5 Gm. of GRISACTIN as from a single dose of 1.0 Gm. of regular griseofulvin. Other blood level studies indicate that with either tablets or capsules, absorption of griseofulvin (microsize) is compar-

3442, 3443, 444

79

able when given in equal amounts as a single dose.

GRISACTIN [griseofulvin (microsize)] has a potent fungistatic action, particularly against those fungi responsible for dermatomycoses in man and animals, namely:

Microsporum canis
M. gypseum
M. audouini
Epidermophyton floccosum
Trichophyton tonsurans
T. rubrum
T. mentagrophytes
T. megnini
T. gallinae
T. verrucosum
T. sulfureum
T. interdigitale
T. schoenleini
T. crateriform

This preparation is not active against:

Candida albicans (monilia)
Cryptococcus neoformans
Blastomyces dermatitidis
Actinomyces israeli
Histoplasma capsulatum
Coccidioides immitis
Malassezia furfur (tinea versicolor) and bacteria

INDICATIONS

Recommended 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)

Prior to the institution of therapy, the type of fungi responsible for the infection should be identified by culture.

CONTRAINDICATIONS

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin. The use of this drug is not justified in minor or trivial infections which will respond to topical antifungal agents alone.

PRECAUTIONS

As with all antibiotics, the use of this drug may result in an overgrowth of nonsusceptible organisms, particularly monilia. Continuing observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken.

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic, and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross-sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Safety of this drug for use in pregnancy has not yet been established.

SIDE EFFECTS

Serious side effects reported with griseofulvin therapy are rare and are usually associated with high dosages and/or long periods of therapy.

Reactions are 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 rarely been reported 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; photosensitivity (patients should be warned to avoid exposure to intense natural or artificial sunlight).

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

ADMINISTRATION AND USUAL DOSAGE

The amount, frequency, and duration of administration are variable, depending on the age of the patient, severity of the infection and practicality of the regimen.

Adults: 0.5 Gm. daily (125 mg. q.i.d., 250 mg. b.i.d., or 500 mg. /day). Patients with less severe or extensive infections may require less, whereas those with widespread lesions may require a starting dose of 0.75 Gm. to 1.0 Gm. a day. This may be reduced gradually to 0.5 Gm. or less after a response has been noted. In all cases, the dosage should be individualized.

Children: A dosage of 10 mg./Kg. daily is usually adequate (children from 30 to 50 lb., 125 mg. to 250 mg. daily; children over 50 lb., 250 mg. to 500 mg.

Edward S. Gajda, Ph.D.
Director, Regulatory Liaison
Agency Laboratories
635 Third Avenue
New York, New York 10017

Dear Dr. Gajda:

We have no objection to the revised package insert submitted on March 6, 1969, for Grisactin (griseofulvin microcaps) in which an addition was made to the "Administration and Usual Dosage" section. This addition was the phrase "or 500 mg./day" in the "Adults" dosage sub-section. The package insert may be put into use.

We have added this labeling to the pending Form 6 files for Grisactin (griseofulvin microcaps) Capsules and Tablets.

Sincerely yours,

I. David Powers
Food and Drug Officer
Office of Certification Services

cc:
WTK-dg
①-100
EC-100/ed
EC-840/Lab
IDPowers:jh

September 8, 1969

Howard E. Guejla, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Guejla:

This is to acknowledge receipt of your letter of August 20, 1969, with which you provided information in accordance with the requirements of 21 CFR 146.14 for the following product:

60-212 (Pending Form 6) - Grisactin (griseofulvin
(necrosine) tablets, 500 mg.)

All future correspondence related to this product should be identified by means of the newly assigned 5-digit number as well as the monograph number.

We will contact you following our review if additional information is necessary.

Sincerely yours,

Milton Eisler
Office of Certification Services

cc:
CC-100
CC-100/OD
Dr. McQueen (MD-140)
SC-840/Lab
MEisler:jh



AYERST LABORATORIES

Pharmaceuticals Through Medical Research

DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Alan E. Smith, M.D.
Alan E. Smith, M.D.

OND
1-28-70
EJN



685 Third Avenue, New York, N. Y. 10017. (212) YUkon 6-1000, Cable: ALPHAMIN, New York

SUPPL NEW CORRES

January 23, 1970

Orig

Marvin Seife, M. D.
Director
Office of Marketed Drugs
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Dr. Seife:

Subject: NDA 60-212 GRISACTIN® [griseofulvin (microsize)] Tablets, 500 mg.

We are writing to advise the Administration that we have adopted a revised system for the assignment of batch and control numbers to this product. The system, detailed in the attached supplement to Part (8) (o) of our New Drug Application, will be put into operation in January, 1970. Our product distribution control procedure, presently on file, remains unchanged. We should like the Administration to include this information in its files for NDA 60-212.

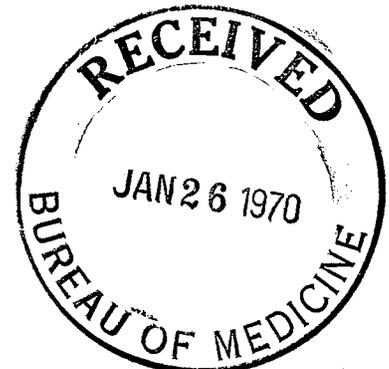
Sincerely,

AYERST LABORATORIES

for Michael M. Fitzpatrick

Howard E. Cmejla, Ph. D.
Director, Regulatory Liaison

HEC:bbg
Enc.



January 28, 1970

Our Reference: #60-212

Howard E. Cmejla, Ph.D.
Director, Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Cmejla:

This is to acknowledge receipt of your submission of January 23, 1970, describing the newly adopted system for assigning batch and control numbers to GRISACTIN [griseofulvin (microsize)] TABLETS, 500 mg. The information presented will be included in our files for Antibiotic Form 6 #60-212

Sincerely yours,

John D. Harrison
Office of Certification Services

cc:

CC-100
CC-100/OD

JDHarrison:dc

AYERST LABORATORIES *Pharmaceuticals Through Medical Research*
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Ayerst®

685 Third Avenue, New York, N. Y. 10017 • (212) YUkon 6-1000 | Cable: ALPHAMIN, New York

February 11, 1970

File

*None reply necessary
JOP 3/12/70*

Mr. I. David Powers
Office of Certification Services
Food and Drug Administration
Washington, D. C. 20204

Dear Mr. Powers:

Subject: NDA 60-212, GRISACTIN® (griseofulvin; microsize) Tablets, 500 mg.,
Physicians Complimentary Dispenser.

Thank you for your comments regarding our draft labeling for a physicians complimentary dispenser for this product given during our February 6th meeting in Washington. As suggested at this meeting, and as indicated in our telephone conversation on January 11th, we plan to make the following changes:

1. Place the expiration date (48 months) and lot number on both the dispenser and blister cartons.
2. Add the word TABLETS following Grisactin® 500, Brand of Griseofulvin (microsize) on the dispenser.
3. A "Usual Dosage" statement will be placed on the dispenser carton since the space available on the blister carton is insufficient for this purpose.

As I mentioned in our telephone conversation we should also like to advise the Administration that on March 4, 1966, in conjunction with a submission for a sample package for Grisactin® [griseofulvin (microsize)] Capsules 250 mg., NDA 13-236, a brochure entitled "Getting around the problem of Ringworm Fungi" was submitted to the Administration and was approved on March 4, 1966 as indicated by a letter from Paul E. Ogles to Ayerst Laboratories. The informational content of the brochure "Some facts on fungal skin infections" submitted to the Administration on February 6, 1970 is identical to the informational content of the aforementioned brochure. Additionally the brochure was submitted as part of a Grisactin 500 physicians sample package to the Bureau of Medicine on April 21, 1969. We hope, therefore, that the presently submitted brochure may be approved without delay.

Mr. I. D. Powers

AYERST LABORATORIES

February 11, 1970

We should further like to advise the Administration that an Antibiotic Form 8 for Grisactin[®] 500 Tablets allowing for the packaging of this product by the (b) (4) for Ayerst Laboratories was submitted to the Office of Certification Services on (b) (4) and approved by the Administration on (b) (4). Repackaging No. (b) (4) was assigned at that time. We should like to ask, therefore, that the Administration disregard the duplicate Antibiotic Form 8 inadvertently submitted for this purpose on February 6, 1970.

Final printed labeling will be submitted to the Administration as soon as it is available. Please accept my thanks for your help in this matter.

Sincerely,

AYERST LABORATORIES

Henry S. Perdue
for

Henry S. Perdue, Ph.D.
Assistant Director,
Regulatory Liaison

HSP:eb
SGS

NDA's: Ayerst, McNeil, Schering
50-051 60-618 60-569
60-210 60-774 (b) (4)
60-212 (b) (4)

March 18, 1970

MEMORANDUM OF CONFERENCE

PRESENT: John Jennings, M.D.)
Alan E. Smith, M.D.) Bureau of Drugs
Max B. McQueen, M.D.) FDA
John Sanders, M.D.)
Jean D. Lockhart, M.D.)
John M. Davitt)
Lorant Buko, D.V.M.)
Richard Norton)

SUBJECT: Griseofulvin

Dr. Smith presented two problems concerning griseofulvin:

1. Particle size. The NAS/NRC report recommended that only the microsize particles be marketed. The reasoning apparently was that the micro form produces higher blood levels. At present, the USP doesn't recognize the large-particle griseofulvin. They refer to the FDA monograph, but there is none.

2. Carcinogenicity. At the December 17, 1969, meeting of the Ad Hoc Committee on the carcinogenicity of griseofulvin, they noted the liver cancers produced in mice, as well as the porphyria noted in animal studies. They recommended labeling changes, as well as encouraging industry to do more studies, especially studies on other, safer, anti-fungal agents. They were especially concerned about long-term, prophylactic use of griseofulvin which has been reported in the troops in Southeast Asia.

Dr. Jennings noted that, before taking the large-particle size product off the market, we need to know more about absorption and tissue levels of both products. The small particle griseofulvin has been shown to be more carcinogenic and may not necessarily be more effective.

Dr. Jennings also inquired about the willingness of the manufacturing firms to do more animal toxicity studies. It was felt the firms would agree. Dr. Jennings then outlined the following course of action:

1. The Division of Anti-infective Drugs should determine what further animal toxicity studies are needed. (If necessary, ask the Ad Hoc Committee again.)

Page 2 - Memo of Conf

2. It should also be determined what human absorption and metabolism studies are needed, comparing the two particle sizes. The statisticians might be helpful in designing such studies.
3. The three manufacturing firms should be convened soon, and asked to do some of these studies. At least a preliminary meeting should be held in the near future.
4. The Federal Register statement on particle size should be deferred for the present.
5. An effort should be made to document the military use of griseofulvin for prophylaxis against fungal infections. When this information has been received, and given to Dr. Jennings in writing, he will contact the Surgeons General to point out that prophylactic use is ill-advised.

Jean D. Lockhart, M.D.
Medical Officer
Division of Anti-infective Drugs

cc:

Orig Form 5
Dup Form 5/BD-240
Trip Form 5
Orig Form 6/BD-240
Dup Form 6/BD-240 60-212
BD-240
BD-140
BD-100
BD-32
Participants
BD-140/JDLockhart/3-19-70
wjs/typed/3-19-70

R/D endorsed by AESmith/BD-140/3-19-70

①

AYERST LABORATORIES Pharmaceuticals Through Medical Research
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION



685 Third Avenue, New York, N. Y. 10017 • (212) YUkon 6-1000/ Cable: ALPHAMIN, New York

OK to sign out
SAP 4/2/70

March 30, 1970

Date 4-6-70

Repacking Permit No. (b) (4)

Mr. Robert C. Brandenburg
Director
Division of Certification Services
Department of Health, Education and Welfare
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Signed *Robert C. Brandenburg*
For the Commissioner of Food and Drugs
Department of Health, Education and Welfare

1555

Dear Mr. Brandenburg:

Subject: NDA 60-212, GRISACTIN® (griseofulvin; microsize) Tablets,
500 mg., Physicians Complimentary Dispenser.

We are transmitting herewith, in triplicate, the final printed labeling for a physicians complimentary dispenser for this product. Please note the labeling has been revised to incorporate the suggestions of the Administration, as outlined at a meeting, between our Dr. Svokos and Mr. Powers of your office, in Washington on February 6, 1970.

We trust the Administration will find the labeling satisfactory and that an early approval is granted so that we may proceed with the preparation and distribution of this sample package as soon as possible.

Your help in expediting this matter would be most appreciated.

We should like the Administration to retain this information in its files for NDA 60-212.

Sincerely,

AYERST LABORATORIES

Henry S. Perdue

Henry S. Perdue, Ph.D.
Assistant Director,
Regulatory Liaison

HSP:eb
SGS
Enc.

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Personally submitted
Dr. Bessert
Pharmaceuticals Through Medical Research.

9/2/70
P. Chagn

685 Third Avenue, New York, N.Y. 10017 • (212) YUkon 6-1000 / Cable: ALPHAMIN, New York

Ab
Bruers.

September 1, 1970

Merle L. Gibson, M.D.
Director
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs
FDA
5600 Fishers Lane
Rockville, Maryland

03735

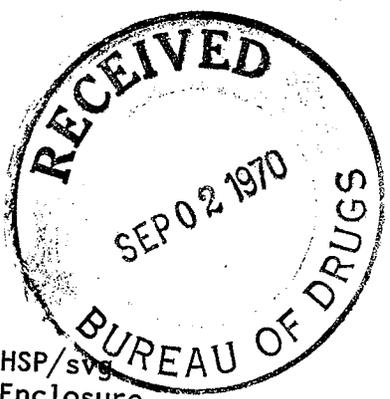
Dear Dr. Gibson:

Subject: NDA 60-212; GRISACTIN® (griseofulvin (microsize)) Tablets,
500 mg.

Enclosed in draft form is a revised package insert for the above product(s). The insert has been revised to include a section on "Animal Studies," as requested by officials of the Administration in a conference with representatives of Ayerst Laboratories, McNeil Laboratories, Inc. and the Schering Corporation on August 12, 1970. In addition, certain of the section headings have been revised in conformance with current policies of the Administration.

The Administration's comments on the draft will be greatly appreciated.

Sincerely,
AYERST LABORATORIES
Henry S. Perdue
Henry S. Perdue, Ph.D.
Assistant Director
Regulatory Liaison



HSP/svs
Enclosure

B 0-145
60-2/2

October 9, 1970

Henry S. Perdue, Ph.D.
Assistant Director
Regulatory Division
Avonnet Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Perdue:

Reference is made to the draft of the revised package insert for GRISEACTIN (griseofulvin (microsize)) TABLETS submitted for review on September 1, 1970. We recommend the following changes in your draft copy:

1. The first section of the insert should include a "Description" statement. You may include anything appropriate under this new section; however the following sentence is sufficient:

"Griseofulvin is an antibiotic derived from a species of Fusillium."

2. The second section should be titled "Actions". Included under this section may be the present introductory text through the clause reading "particularly against those fungi responsible for dermatomycoses in man and animals". (The word "namely" should be deleted).

3. The third section should be titled "Indications" and set up as follows:

"Recommended 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)

Note: Prior to the institution of 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 antifungal agents alone.

(b) (4)

This preparation is not active against:

(List organisms mentioned on top of page 2 of draft).

4. The last sentence should be deleted from the fourth section "Contraindications".

5. After "Contraindications" a new section should be inserted to read:

"WARNINGS"

Usage in Pregnancy: Safety for use of this drug in pregnancy has not been established.

Safety and efficacy of the prophylactic use of this drug has not been established.

(b) (4)

6. Under the Precautions section replace the last sentence with the following:

"Patients should be (b) (4) to avoid exposure to intense natural or artificial (b) (4)

(b) (4)

(b) (4)

eliminates usually decrease griseofulvin activity".

7. On page 3 of the draft, under "Adverse Reactions", delete the parenthetical clause at the end of the second paragraph since such information is to be included under "Precautions".

Please send three copies of the revised insert as soon as they are available in final printed form. We recommend that a limited number of the revised inserts be printed at this time since further labeling

Page 3-- Dr. Perdue

revisions may be required when the HAS/NEC recommendations on griseofulvin are announced in the FEDERAL REGISTER.

Sincerely yours,

John D. Harrison
Certification Services Branch
Division of Anti-Infective Drug Products

cc:

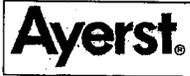
Dr. Graves: M-230

BD-145

BD-145/OD

BD-430/Lab.

JDHarrison:hb



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

H 6
[Handwritten signature]

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

November 10, 1970

Merle L. Gibson, M. D.
Director
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Gibson:

Subject: NDA 60-212; GRISACTIN® [griseofulvin (microsize)] Tablets, 500 mg.
NDA 50-051; GRISACTIN® [griseofulvin (microsize)] Capsules, 125 and 250 mg.

Enclosed in draft form is a second revision of the package insert for the above products. The first revision was submitted to the Administration on September 1, 1970. The second revision reflects changes recommended by the Administration as stated in a letter from Mr. John D. Harrison, dated October 9, 1970. We hope the Administration will find this insert acceptable so that we may initiate printing as soon as possible.

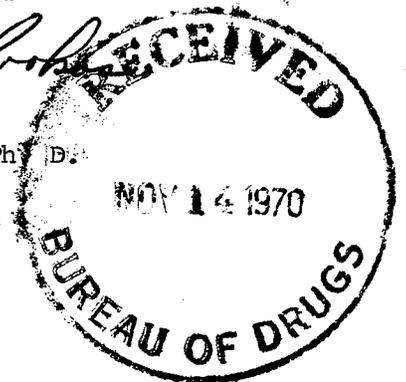
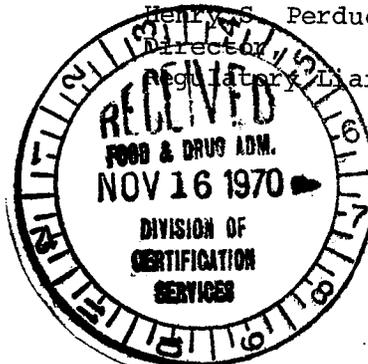
Six copies of the draft insert have been enclosed so that copies may be filed in both NDA 60-212 and NDA 50-051.

Sincerely,

AYERST LABORATORIES

Steve H. [Handwritten signature]
for

Henry S. Perdue, Ph.D.
Director
Regulatory Liaison



1970

HSP/mbd
SGS
Encls.

November 18, 1970

Our reference:

60-212

50-051

60-210

Henry S. Perdue, Ph. D.
Director,
Regulatory Liaison
Ayerst Laboratories
685 Third Avenue
New York, New York 10017

Dear Dr. Perdue:

The revised package inserts submitted in draft form with your letters of November 10, 1970 for Grisactin (griseofulvin microsize) Tablets and Capsules and Griseofulvin (regular size) Tablets are satisfactory with the exception of the following:

There should be a period rather than a comma after the last word (animals) in the "Actions" section of the Grisactin insert.

When these inserts are available in final printed form, please submit three copies of each for approval.

Sincerely yours,

I. David Powers
Certification Services Branch
Division of Anti-Infective Drug Products

cc:

BD-145 (3) ✓

BD-145/OD

BD-430/lab.

IDPowers:hb



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Hand del by Dr Swobas. 6-20-72 12/6/71 WTR/KP. AG Mager

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

December 6, 1971

Mr. William T. Robinson
Certification Services Staff
Division of Anti-Infective Drug Products
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Date Approved 6/20/72
Account No. _____
Signed [Signature]
For the Commissioner of Food and Drugs
Department of Health, Education and Welfare

Dear Mr. Robinson:

SUBJECT: NDA 60-212, GRISACTIN® (griseofulvin (microsize)) Tablets

As requested by the Administration we are submitting, in triplicate, an updated Form 6 for GRISACTIN® (griseofulvin (microsize)) Tablets. Consideration has been given to the recommendations appearing in your letter of October 1, 1971 and these have been incorporated into the enclosed Form 6.

(b) (4) is in the process of completing an Antibiotic Form 4 for shipment of (b) (4) griseofulvin to Ayerst Laboratories, Rouses Point, N.Y. When we have received the completed form, it will immediately be forwarded to the Administration. In addition, we are also in the process of obtaining up-dated Antibiotic Form 4's from (b) (4) and the (b) (4) of (b) (4). Again these will be forwarded to the Administration as soon as they have been completed.

A Form 8, allowing for the repackaging of GRISACTIN® (griseofulvin (microsize)) Tablets by the (b) (4) of (b) (4), was submitted to the Administration on (b) (4) and was approved on (b) (4). Repackaging Permit No. (b) (4) was assigned. Since this is already on file with the Administration we have not enclosed a copy herein.

In response to Item No. 3 of your October 1, 1971 letter, in process controls are contained in Parts 3f, 3g, 3h, 3n, and 3o of the enclosed Form 6.

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

Sincerely,

AYERST LABORATORIES

[Signature]

Henry S. Perdue, Ph.D.
Director, Regulatory Affairs



January 5, 1972

Our reference:

50-051

60-212

Ayerst Laboratories, Inc.
Attention: Dr. Henry S. Perdue
Director, Regulatory Liaison
685 Third Avenue
New York, New York 10017

Gentlemen:

This will acknowledge receipt of your updated Form 6's dated December 2, 1971, for Grisactin (griseofulvin) capsules and for Grisactin (griseofulvin) tablets dated December 6, 1971. We have the following comments:

1. Under paragraph 3(b) of your Form 6's, information should be provided regarding the accountability of batches of (b)(4) griseofulvin. The Form 6's should give sufficient details to correlate (b)(4) (b)(4) batch numbers of the (b)(4) griseofulvin to your batch numbers on the microsize griseofulvin sent into FDA for testing. We note that the size of the batches of (b)(4) griseofulvin shipped by (b)(4) are considerably different from the size batches you submit to FDA. If these batches of (b)(4) griseofulvin are not (b)(4) is part of your procedure, then this information should be incorporated in the Form 6's. Copies of the forms used to record these correlations should be submitted.
2. The method of assay used by Ayerst to determine the potency of the microsize griseofulvin should be specified in the Form 6.
3. Since your firm has quality control laboratories in two different locations, the Form 6 should state at which location, the various monograph tests are conducted.
4. The Form 6 does not contain a complete description of the methods and processes used in manufacturing the drug. Copies of the master formulas for both the capsules and the tablets, complete with manufacturing directions should be submitted.
5. In process controls are not well defined. We expect the Form 6 to reflect all in process controls and the limits/specifications of these controls.

Page 2

6. The method of assay used by Ayerst to determine the potency of the griseofulvin capsules and tablets should be specified in the Form 6.

7. Stability data should include time and temperature as submitted, however, the type of drug container e.g. glass or polyethylene and other pertinent information such as light and humidity should also be included in the studies on drug stability.

Further consideration will be given your Form 6 submissions on griseofulvin products on receipt of the above requested information.

Sincerely yours,

William E. Wagner
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug
Products

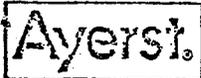
cc:

BD-145

BD-145/OD

BD-430/Lab

WEWagner:rl:1-5-72



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

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

March 23, 1972

William E. Magner
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 50-051, GRISACTIN® (griseofulvin (microsize)) Capsules
NDA 60-212, GRISACTIN® (griseofulvin (microsize)) Tablets

Dear Mr. Magner:

The Administration's letter of January 5, 1972 requested additional information in regard to the updated FORMS -6 submitted to your office on December 6, 1971. The information requested has been assembled by our Mr. ^{(b) (6)} and is enclosed herein for your review. Your early consideration of this material would be appreciated.

Please include this information in the Administration's files for NDA 50-051 and NDA 60-212.

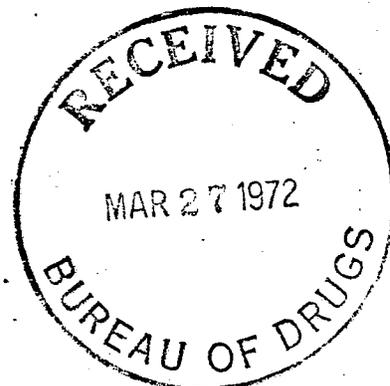
Sincerely,

AYERST LABORATORIES

for
Henry S. Perdue

Henry S. Perdue, Ph.D.
Director, Regulatory Affairs

HSP
SGS:cb
Encl.





BD-145

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852
March 31, 1972

Our reference:

- 50-051 ✓ cap micro
- 60-212 ✓ micro
- 60-210 - CT reju/ol (nowbit)

[Redacted] (b) (4)

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

Gentlemen:

This is in reference to your up-dated Form 6 dated December 2, 1971, amended March 23, 1972 to provide for the certification of Grisactin (griseofulvin microsize) Capsules and Grisactin (griseofulvin microsize) Tablets. We have the following comments:

1. The amendment dated March 23, 1972, refers to the receipt of the microsize griseofulvin from [Redacted] (b) (4). The submission states the material is subjected to testing and then released [Redacted] (b) (4).

[Redacted] (b) (4)

(c) Please explain how and when the batches are sampled that are submitted to FDA.

2. [Redacted] (b) (4)

Our position is that

(b) (4)

We are requesting that Ayerst

(b) (4)

Please be advised that

(b) (4)

Sincerely yours,

William E. Magner
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products

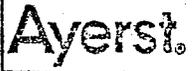
cc:

BD-145

BD-145/OD

BD-430/lab.

WEMagner:hb



AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

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

May 8, 1972

William E. Magner
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland

Dear Mr. Magner:

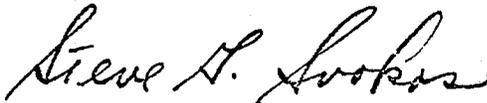
Subject: NDA 50-051, GRISACTIN® (griseofulvin) Capsules
NDA 60-212, GRISACTIN® (griseofulvin) Tablets

The Administration's letter of March 31, 1972 requested, in part, additional information in support of the up-dated FORMS -6 for the above mentioned products. The additional information has been obtained and is detailed in the attached memorandum from our Mr. ^{(b) (6)}. We trust we have now satisfactorily answered all of the Administration's questions in regard to our two GRISACTIN FORMS -6.

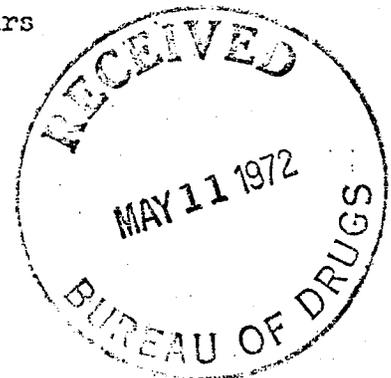
Please include this information in the Administration's files for NDA 50-051 and NDA 60-212.

Sincerely,

AYERST LABORATORIES

for 
Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
SGS:cb
#1.



OCS Review Form 6 Addendum

#60-212

#50-051

Griseofulvin Tablets and Capsules

Ayerst Laboratories

New York, New York

The firm submitted the additional material requested in our letter of January 5, 1972.

On June 7 and 8, 1972, I visited Ayerst Laboratories in Rouses Point, New York.

The firm was found to be operating essentially as specified in the Form 6.

(b) (4)



WEM

William E. Megner BD-145
June 19, 1972