CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-414

Generic Name: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

Sponsor: G & W Laboratories, Inc.

Approval Date: April 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74-414

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EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	X
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Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

APPROVAL LETTER

ANDA 74-414

APR 20 1997

G & W Laboratories, Inc.
Attention: Kripanath Borah, Ph.D.
111 Coolidge Street
South Plainfield, New Jersey 07080

Dear Dr. Borah:

This refers to your abbreviated new drug application dated October 8, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendments dated May 12 and September 5, 1995, March 15 and May 16, 1996, and March 21, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Miconazole Nitrate Vaginal Suppositories USP, 100 mg to be bioequivalent to the listed drug, Monistat® 7 Vaginal Suppositories, 100 mg, of RW Johnson Pharmaceutical Research Institute.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

/S/

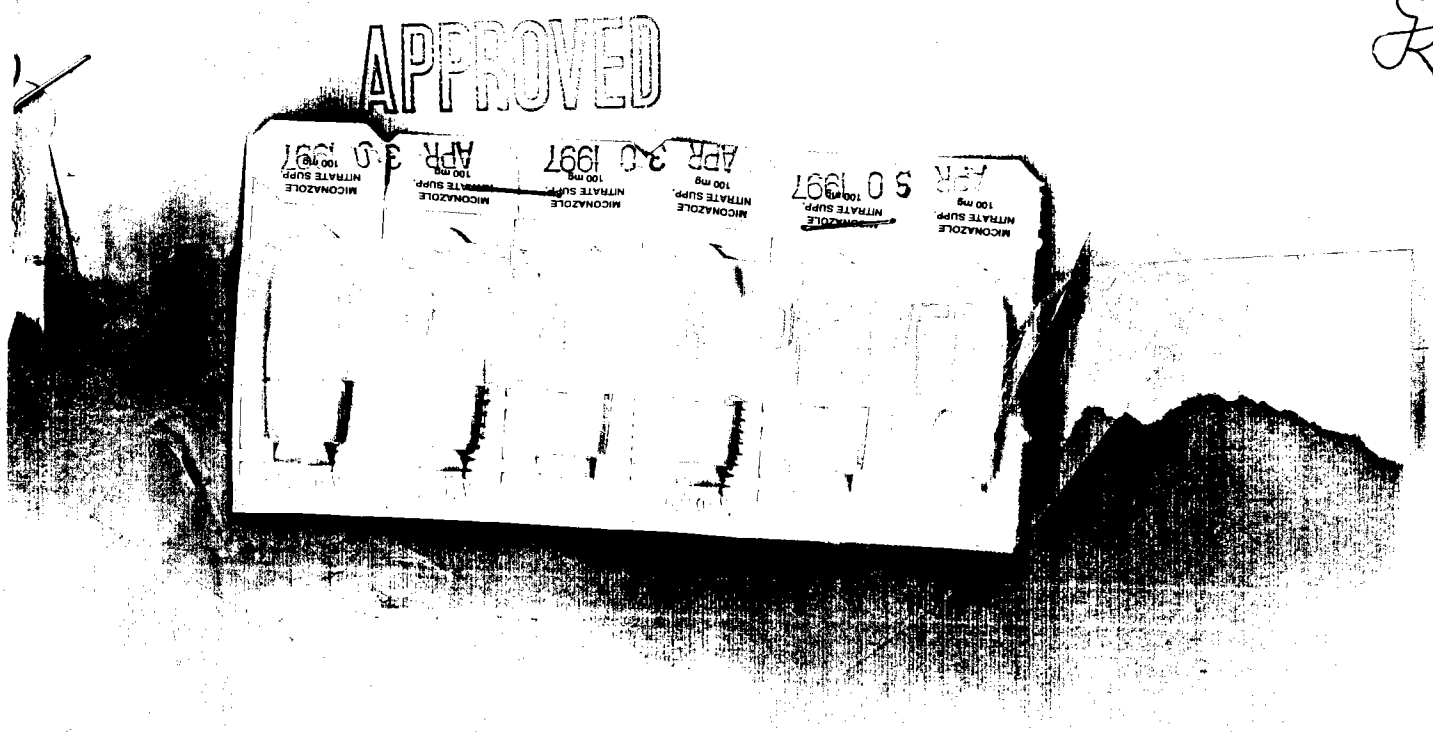
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

Final Printed Labeling


APPROVED
MICONAZOLE NITRATE SUPP. 100 mg
APR 30 1997

EDUCATIONAL BROCHURE

APPROVED

MICONAZOLE NITRATE

VAGINAL SUPPOSITORIES USP, 100 MG

CURES MOST VAGINAL YEAST INFECTIONS

INDICATION:
For the treatment of vaginal yeast infections (candidiasis).

If you have any or all of the symptoms of a yeast infection (vaginal burning, discharge) and if at some time in the past your doctor told you that these symptoms are due to a yeast infection, then miconazole nitrate vaginal suppositories USP, 100 mg should work for you. If, however, you have never had these symptoms before, you should see your doctor before using miconazole nitrate vaginal suppositories USP, 100 mg.

MICONAZOLE NITRATE VAGINAL SUPPOSITORIES USP, 100 MG ARE FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS ONLY. THEY DO NOT TREAT OTHER INFECTIONS AND DO NOT PREVENT PREGNANCY.

WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?
A yeast infection is a common type of vaginal infection. Your doctor may call it candidiasis. This condition is caused by an organism called *Candida*, which is a type of yeast. Even healthy women usually have this yeast on the skin, in the mouth, in the digestive tract, and in the vagina. At times, the yeast can grow very quickly. In fact, the infection is sometimes called yeast (*Candida*) "overgrowth".

A yeast infection can occur at almost any time of life. It is most common during the childbearing years. The infection tends to develop most often in some women who are pregnant, diabetic, taking antibiotics, taking birth control pills, or have a damaged immune system.

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV - the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you may have been exposed to HIV and are now experiencing either frequently recurring vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE AT 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7899 (hearing impaired, TDD).

IF YOU EXPERIENCE FREQUENT YEAST INFECTIONS (THEY RECUR WITHIN A TWO MONTH PERIOD) OR IF YOU HAVE YEAST INFECTIONS THAT DO NOT CLEAR UP EASILY WITH PROPER TREATMENT, YOU SHOULD SEE YOUR DOCTOR PROMPTLY TO DETERMINE THE CAUSE AND TO RECEIVE PROPER MEDICAL CARE.

SYMPTOMS OF VAGINAL YEAST INFECTIONS
There are many signs and symptoms of a yeast infection. They can include:

- ☐ Vaginal itching (ranging from mild to intense);
- ☐ A clumpy, vaginal discharge that may look like cottage cheese;
- ☐ Vaginal soreness, irritation or burning, especially during intercourse;
- ☐ Rash or redness around the vagina (vulvar irritation).

NOTE: Vaginal discharge that is different from above, for example, a yellow/green discharge or a discharge that smells "fishy", may indicate that you have something other than a yeast infection. If this is the case, you should consult your doctor before using miconazole nitrate vaginal suppositories USP, 100 mg.

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast. Do not use in eyes or take by mouth.
- **DO NOT USE MICONAZOLE NITRATE VAGINAL SUPPOSITORIES USP, 100 MG IF YOU HAVE ANY OF THE FOLLOWING SIGNS AND SYMPTOMS. ALSO, IF THEY OCCUR WHILE YOU ARE USING MICONAZOLE NITRATE VAGINAL SUPPOSITORIES USP, 100 MG STOP USING THE PRODUCT AND CONTACT YOUR DOCTOR RIGHT AWAY. YOU MAY HAVE A MORE SERIOUS ILLNESS.**

Fever (Above 100°F orally)
Pain in the lower abdomen, back or either shoulder
A vaginal discharge that smells bad

- If there is no improvement or if the infection worsens within 3 days, or complete relief is not felt within 7 days, or your symptoms return within two months, then you may have something other than a yeast infection. You should consult your doctor.
- If you may have been exposed to the human immunodeficiency virus (HIV, the virus that causes AIDS) and are now having recurrent vaginal infections, especially infections that don't clear up easily with proper treatment, see your doctor promptly to determine the cause of your symptoms and to receive proper medical care.
- Hydrogenated vegetable oil may weaken latex in condoms or in diaphragms. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using miconazole nitrate vaginal suppositories USP, 100 mg.
- Do not use tampons while using this medication.
- Do not use in girls less than 12 years of age.
- If you are pregnant or think you may be, do not use this product except under the advice and supervision of a doctor.
- Keep this and all drugs out of the reach of children.
- In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

CONTENTS
Seven vaginal suppositories each containing 100 mg miconazole nitrate. One plastic applicator.

IMPORTANT: EACH SUPPOSITORY IS INDIVIDUALLY WRAPPED. IF A SUPPOSITORY IS UNWRAPPED OR THERE ARE SIGNS OF TAMPERING, DO NOT USE. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

FULL PRESCRIPTION STRENGTH

MICONAZOLE NITRATE

VAGINAL SUPPOSITORIES USP, 100 mg

NDC 0713-0197-57

FULL PRESCRIPTION STRENGTH

MICONAZOLE NITRATE

VAGINAL SUPPOSITORIES USP, 100 mg

CURES MOST VAGINAL YEAST INFECTIONS

Contains 7 Vaginal Suppositories

APPROVED

ACTIVE INGREDIENT: miconazole nitrate (100 mg per suppository).
INACTIVE INGREDIENT: hydrogenated vegetable oil base.
Store at room temperature 15-30°C (59-86°F).
Avoid heat over 30°C (86°F).

G&W Labs Inc.
S. Plainfield, N.J.
07080

SATISFACTION OR YOUR MONEY BACK FROM G&W GUARANTEED

Until now, you could not buy miconazole nitrate vaginal suppositories USP, 100 mg without a prescription. They are a cure for most vaginal yeast infections.

INDICATION: For the treatment of vaginal yeast infections (candidiasis).

IF THIS IS THE FIRST TIME YOU HAVE HAD VAGINAL ITCH AND DISCOMFORT, CONSULT YOUR DOCTOR. IF YOU HAVE HAD A DOCTOR DIAGNOSE A VAGINAL YEAST INFECTION BEFORE AND HAVE THE SAME SYMPTOMS NOW, USE THESE SUPPOSITORIES AS DIRECTED FOR SEVEN CONSECUTIVE DAYS.

FOR VAGINAL USE ONLY. DO NOT USE IN EYES OR TAKE BY MOUTH.

DIRECTIONS: Insert one suppository high into the vagina at bedtime for seven nights in a row. Applicator and instructions are enclosed. Before using, read the enclosed brochure.

WARNINGS: DO NOT USE MICONAZOLE NITRATE VAGINAL SUPPOSITORIES USP, 100 MG IF YOU HAVE ANY OF THE FOLLOWING SIGNS AND SYMPTOMS. ALSO, IF THEY OCCUR WHILE USING MICONAZOLE NITRATE VAGINAL SUPPOSITORIES USP, 100 MG, STOP USING THE PRODUCT AND CONTACT YOUR DOCTOR RIGHT AWAY. YOU MAY HAVE A MORE SERIOUS ILLNESS. • FEVER (HIGHER THAN 100°F ORALLY) • PAIN IN THE LOWER ABDOMEN, BACK, OR EITHER SHOULDER • A VAGINAL DISCHARGE THAT SMELLS BAD. IF YOU DO NOT IMPROVE IN 3 DAYS, OR IF YOU DO NOT GET WELL IN 7 DAYS, YOU MAY HAVE A CONDITION OTHER THAN A YEAST INFECTION. CONSULT YOUR DOCTOR. If your symptoms return within two months or if you have infections that do not clear up easily with proper treatment, consult your doctor. You could be pregnant or there could be a serious underlying medical cause for your infections, including diabetes or a damaged immune system (including damage from infection with HIV - the virus that causes AIDS). (PLEASE READ EDUCATIONAL BROCHURE FOUND WITHIN PACKAGE).

Hydrogenated vegetable oil may weaken latex in condoms or in diaphragms. These suppositories contain hydrogenated vegetable oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using miconazole nitrate vaginal suppositories USP, 100 mg. • Do not use tampons while using this medication. • DO NOT USE IN GIRLS LESS THAN 12 YEARS OF AGE. • If you are pregnant or think you may be pregnant, do not use this product except under the advice and supervision of a doctor. • Keep this and all drugs out of the reach of children. • In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

TAMPER RESISTANT: EACH SUPPOSITORY IS INDIVIDUALLY WRAPPED. IF A SUPPOSITORY IS UNWRAPPED OR THERE ARE SIGNS OF TAMPERING, DO NOT USE. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

10-19757GW1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 74-414

3. NAME AND ADDRESS OF APPLICANT
G & W Laboratories, Inc
111 Coolidge Street
South Plainfield, NJ 07080

4. LEGAL BASIS OF SUBMISSION:
No Patent or any marketing exclusivity rights are in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Miconazole Nitrate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Applicant:

10/08/93	Original Submission
12/06/93	Amendment

FDA:

11/16/93	Refuse to file
12/22/93	Acceptable filing

10. PHARMACOLOGICAL CATEGORY
Antifungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Reference Drug: Miconazole Nitrate Vaginal Suppositories (Monistat®7) 100 mg
Holder: R. W. Johnson
NDA # 17450

DMF #/Type	HOLDER	SUBJECT	STATUS
[redacted]	[redacted]	Miconazole Nitrate USP	Sat
[redacted]	[redacted]	[redacted]	Def

13. DOSAGE FORM
Suppositories (Vaginal)

14. STRENGTH
100 mg

15. CHEMICAL NAME AND STRUCTURE
1H-Imidazole, 1-[2-(2,4-dicholrophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate.
Mol formula $C_{18}H_{14}Cl_4N_2O.HNO_3$ Mol Wt 479.15

16. COMMENTS
Deficiencies are in the following area: Manufacturing and processing, laboratory controls, containers/closures, raw material and stability.

17. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable.

18. RECORDS AND REPORTS
N/A

19. REVIEWER: DATE COMPLETED:
Vilayat A. Sayeed, Ph.D. 1/5/93

Endorsed by P.Schwartz, Ph.D. 2-24-94

APPEARS THIS WAY
ON ORIGINAL

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pages of trade secret and/or confidential commercial information

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-414

3. NAME AND ADDRESS OF APPLICANT
G & W Laboratories, Inc
111 Coolidge Street
South Plainfield, NJ 07080

4. LEGAL BASIS OF SUBMISSION:
No Patent or any marketing exclusivity rights are in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Miconazole Nitrate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Applicant:

10/08/93	Original Submission
12/06/93	Amendment
06/03/94	Amendment

FDA:

11/16/93	Refuse to file
12/22/93	Acceptable filing
03/02/94	NA Letter

10. PHARMACOLOGICAL CATEGORY
Antifungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Reference Drug:	Miconazole Nitrate Vaginal Suppositories (Monistat®7) 100 mg
Holder:	R. W. Johnson
NDA #	17450

For DMF's details please refer to item #37 of this review.

13. DOSAGE FORM
Suppositories (Vaginal)

14. STRENGTH
100 mg

15. CHEMICAL NAME AND STRUCTURE
1H-Imidazole, 1-[2-(2,4-dicholrophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate.
Mol formula $C_{18}H_{14}Cl_4N_2O.HNO_3$ Mol Wt 479.15

16. COMMENTS

17. CONCLUSIONS AND RECOMMENDATIONS

18. RECORDS AND REPORTS
N/A

19. REVIEWER: DATE COMPLETED:
Vilayat A. Sayeed, Ph.D. 10-7-94

Endorsed by P. Schwartz, Ph.D. 10-7-94

APPEARS THIS WAY
ON ORIGINAL

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OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-414

3. NAME AND ADDRESS OF APPLICANT
G & W Laboratories, Inc
111 Coolidge Street
South Plainfield, NJ 07080

4. LEGAL BASIS OF SUBMISSION:
No Patent or any marketing exclusivity rights are in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Miconazole Nitrate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Applicant:

10/08/93	Original Submission
12/06/93	Amendment
06/03/94	Amendment
01/03/95	Amendment
05/12/95	Amendment
08/11/95	Amendment
09/05/95	Amendment

FDA:

11/16/93	Refuse to file
12/22/93	Acceptable filing
03/02/94	NA Letter
10/21/95	NA Letter
02/08/96	NA Letter (Bio)

10. PHARMACOLOGICAL CATEGORY
Antifungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Reference Drug: Miconazole Nitrate Vaginal Suppositories (Monistat®7) 100 mg
Holder: R. W. Johnson
NDA # 17450
For DMF's details please refer to item #37 of this review.

13. DOSAGE FORM
Suppositories (Vaginal)

14. STRENGTH
100 mg

15. CHEMICAL NAME AND STRUCTURE
1H-Imidazole, 1-[2-(2,4-dicholrophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate.
Mol formula $C_{18}H_{14}Cl_4N_2O.HNO_3$ Mol Wt 479.15

16. COMMENTS
The deficiencies are Bioequivalance.

17. CONCLUSIONS AND RECOMMENDATIONS
The application remains not approvable

18. RECORDS AND REPORTS
N/A

19. REVIEWER: DATE COMPLETED:
Vilayat A. Sayeed, Ph.D. 2/22/96

Endorsed by P. Schwartz, Ph.D. 2/28/96

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1. CHEMIST'S REVIEW NO.4

2. ANDA # 74-414

3. NAME AND ADDRESS OF APPLICANT

G & W Laboratories, Inc
111 Coolidge Street
South Plainfield, NJ 07080

4. LEGAL BASIS OF SUBMISSION:

No Patent or any marketing exclusivity rights are in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Miconazole Nitrate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

10/8/93	Original Submission
12/06/93	Amendment
6/3/94	Amendment
1/3/95	Amendment
3/8/95	Amendment
5/12/95	Amendment
9/5/95	Amendment
5/16/96	Amendment
3/21/97	Amendment

10. PHARMACOLOGICAL CATEGORY

Antifungal

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

Reference Drug: Miconazole Nitrate Vaginal Suppositories (Monistat®7) 100 mg
Holder: R. W. Johnson
NDA # 17-450

DMF #/Type	HOLDER	SUBJECT	STATUS
[redacted]	[redacted]	[redacted]	Sat.
[redacted]	[redacted]	[redacted]	Sat.

13. DOSAGE FORM

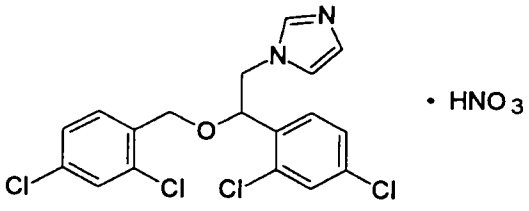
Suppository (Vaginal)

14. STRENGTH

100 mg

15. CHEMICAL NAME AND STRUCTURE

Miconazole Nitrate. $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$. 479.15. 1*H*-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate. 22832-87-7. Antifungal. USP 23, page 1026.



16. COMMENTS

17. CONCLUSIONS AND RECOMMENDATIONS

The application is Approvable.

19. REVIEWER: /S/

Nashed E. Nashed, Ph.D.

DATE COMPLETED: 3/28/97

3/24/97

Endorsed by P. Schwartz, Ph.D.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-414 SPONSOR: G&W Laboratories, Inc..

DRUG AND DOSAGE FORM: Miconazole Nitrate Vaginal Suppository

STRENGTHS(s): 100 mg

TYPE OF STUDY: Comparative Clinical Study

STUDY SITE: [redacted]

STUDY SUMMARY: Bioequivalence between the test and reference (Ortho's, Monistat-7® Vaginal creams) products was determined on the basis of comparative clinical study. The medical and statistical evaluations indicate, that on the third visit, mycologic, clinical and therapeutic cure rates for G&W and Ortho miconazole nitrate vaginal suppositories were equivalent, and the products met the criteria of 90% confidence interval of 80-120%. No serious adverse reactions were observed.

G&W Laboratories and Ortho's, miconazole nitrate vaginal suppositories are qualitatively and quantitatively different. [redacted] are hydrogenated vegetable oils. While the excipient [redacted] is within the IIG limits, [redacted] is not listed in the IIG (1996). However, [redacted] as been used in approved application (ANDA 73-507, miconazole nitrate vaginal Suppository) [redacted] mg/suppository). Since it is a hydrogenated vegetable oil, and in clinical study no side effects were noted, product should be safe.

The study was found acceptable by the Division of Anti-Infective Drug Products, Biometrics Division, and by the Division of Bioequivalence.

DISSOLUTION: Not required.

PRIMARY REVIEWER: S.P.Shrivastava, Ph.D. BRANCH: II

INITIAL: /S/ DATE 3/5/97

BRANCH CHIEF: Shriniwas. G.Nerurkar, Ph.D. BRANCH: II

INITIAL: /S/ DATE 3/6/1997

for DIRECTOR
DIVISION OF BIOEQUIVALENCE: Nicholas M. Fleischer, Ph.D.

INITIAL: /S/ DATE 3/6/97

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL /S/ DATE 3/11/97

FEB 3 1997

ANDA # 74-414
Miconazole Nitrate Vaginal Suppositories, 100 mg
Reviewer: S. P. Shrivastava
WP # 74414S.596

G&W Laboratories, Inc.
South Plainfield, NJ
Submission Date:
May 16, 1996

REVIEW OF A BIOEQUIVALENCE STUDY

The firm had submitted a comparative clinical study, dated 10/8/93 and amendments, dated 5/12/95 and 9/5/95, for its OTC drug product miconazole nitrate vaginal suppositories, 100 mg, which was sent for consult to the Division of Anti-Infective Drug Products (HFD-520), and to the Biometrics Division (HFD-725).

In the initial review, the product did not meet the bioequivalence criteria and the application was considered not acceptable (Re: review by Henderson, 1/30/96). The firm had assessed the patients at two post-treatment visits, Visit 2 (study days 14-17) and Visit 3 (study days 35-42). But the reviewing Medical Officer extended the evaluation period to include weekends and holidays. Thus Visit 2 and Visit 3 included study days 13-18 and 34-43, respectively. While the firm was informed of the outcome of the study (OGD letter, dated 2/8/96), the Medical Officer also requested amendments and additional data directly from the firm for re-evaluation. This re-review includes the additional data provided by the firm.

The medical and statistical reviews were carried out by Drs. Julius Piver, Ralph Harkins and Daphne Lin, and were concurred by Drs. Brad Leissa and David Feigal (Attachments 1-4). According to the reviewers, the generic vaginal suppositories must meet the 90% confidence interval and the therapeutic cure rates (combined mycological and clinical cure rate) should be 80-120%. The medical and statistical evaluations indicated, that on Visit 3, mycologic cure rates (76 vs. 79%) and clinical cure rates (85 vs 92%) for G&W and Ortho's miconazole nitrate vaginal suppositories are equivalent. However, the therapeutic cure rates (69 vs. 77%; 90% CI =75.9-107.5) for the two products were not equivalent. Therefore, G&W's miconazole nitrate vaginal suppository were considered not bioequivalent to the Ortho's Monistat-7^{R} by the reviewers.

Dr. Piver et al. reviews, however, were reexamined by Drs. Mary Fanning and Brad Leissa, and certain mistakes were found. Among other things, it was found that in case of Ortho product, Patients #15, 32, and 79 should have been therapeutic failure rather than cure. The correction narrowed the difference in therapeutic cure rates between the test and reference products (69.1 vs. 71.7%), and the 90% confidence interval also fell within the required 80-120% range (81.09 - 113.69%). The evaluation has been concurred by Dr. David Feigal (see E-mails, Attachments 5-9), and the product now meets the *in vivo* bioequivalence criteria.

Comparative composition of the formulations are given in Table 1. The test product differs qualitatively and quantitatively from the reference product. [redacted] and [redacted] are hydrogenated vegetable oils. While the excipient [redacted] is within the IIG limits, [redacted] is not listed in the IIG (1996). However, [redacted] has been used in approved application

(ANDA 73-507, miconazole nitrate vaginal Suppository) [redacted] mg/suppository). Since it is a hydrogenated vegetable oil, and in clinical study no side effects were noted, product should be safe.

COMMENTS

1. The firm should develop dissolution methods and specifications, submit the data to the agency at the earliest, and use them as quality control tool.

2. Summary report, IRB approval letter, drug composition, and product formulation data did not document the product Lot # used in the study. Lot # 0197-PB-13-A for test and Lot #11D317 for Ortho product were recorded only in the clinical report. In future, the firm should document the Lot # of the products adequately.

3. There are three evaluable parameters considered by the Medical Officer at FDA: clinical cure rate, mycological cure rate, and therapeutic cure rate. The medical and statistical evaluations indicate, that on the third visit, mycologic, clinical and therapeutic cure rates for G&W and Ortho miconazole nitrate vaginal suppositories are equivalent. The parameter values were obtained at second (V2) and third (V3) visits, and were statistically analyzed using 90% CI criteria.

RECOMMENDATION

The comparative clinical study conducted by G&W Laboratories, Inc., on its miconazole nitrate vaginal suppositories, 100 mg, Lot # 0197-PB-13-A, comparing it to Ortho's Monistat-7, 100 mg, Lot #11D317 has been found acceptable by the Division of Anti-Infective Drug Products, and by the Division of Bioequivalence. The study demonstrates that G&W Laboratories' miconazole nitrate vaginal suppository, 100 mg, is bioequivalent to the reference product, Monistat-7^{R}, 100 mg, manufactured by Ortho.

The firm should be informed of the comments #1-2 and the recommendation.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar /S/ Date 1/30/1997

(NOT TO BE RELEASED UNDER F.O.I.)

Table 1. Comparative Formulation

Ingredients	G&W Labs. mg/Suppository	Ortho USA mg/Suppository
Miconazole nitrate, USP	100	100
Hydrogenated Vegetable Oil	---	PNG[1]

[1] Potency Not Given

FEB 3 1997

ANDA # 74-414
Miconazole Nitrate Vaginal Suppositories, 100 mg
Reviewer: S. P. Shrivastava
WP # 74414S.596

G&W Laboratories, Inc.
South Plainfield, NJ
Submission Date:
~~**May 16, 1996**~~
March 15, 1996

REVIEW OF A BIOEQUIVALENCE STUDY

The firm had submitted a comparative clinical study, dated 10/8/93 and amendments, dated 5/12/95 and 9/5/95, for its OTC drug product miconazole nitrate vaginal suppositories, 100 mg, which was sent for consult to the Division of Anti-Infective Drug Products (HFD-520), and to the Biometrics Division (HFD-725).

In the initial review, the product did not meet the bioequivalence criteria and the application was considered not acceptable (Re: review by Henderson, 1/30/96). The firm had assessed the patients at two post-treatment visits, Visit 2 (study days 14-17) and Visit 3 (study days 35-42). But the reviewing Medical Officer extended the evaluation period to include weekends and holidays. Thus Visit 2 and Visit 3 included study days 13-18 and 34-43, respectively. While the firm was informed of the outcome of the study (OGD letter, dated 2/8/96), the Medical Officer also requested amendments and additional data directly from the firm for re-evaluation. This re-review includes the additional data provided by the firm.

The medical and statistical reviews were carried out by Drs. Julius Piver, Ralph Harkins and Daphne Lin, and were concurred by Drs. Brad Leissa and David Feigal (Attachments 1-4). According to the reviewers, the generic vaginal suppositories must meet the 90% confidence interval and the therapeutic cure rates (combined mycological and clinical cure rate) should be 80-120%. The medical and statistical evaluations indicated, that on Visit 3, mycologic cure rates (76 vs. 79%) and clinical cure rates (85 vs 92%) for G&W and Ortho's miconazole nitrate vaginal suppositories are equivalent. However, the therapeutic cure rates (69 vs. 77%; 90% CI =75.9-107.5) for the two products were not equivalent. Therefore, G&W's miconazole nitrate vaginal suppository were considered not bioequivalent to the Ortho's Monistat-7^{R} by the reviewers.

Dr. Piver et al. reviews, however, were reexamined by Drs. Mary Fanning and Brad Leissa, and certain mistakes were found. Among other things, it was found that in case of Ortho product, Patients #15, 32, and 79 should have been therapeutic failure rather than cure. The correction narrowed the difference in therapeutic cure rates between the test and reference products (69.1 vs. 71.7%), and the 90% confidence interval also fell within the required 80-120% range (81.09 - 113.69%). The evaluation has been concurred by Dr. David Feigal (see E-mails, Attachments 5-9), and the product now meets the *in vivo* bioequivalence criteria.

Comparative composition of the formulations are given in Table 1. The test product differs qualitatively and quantitatively from the reference product. [redacted] and [redacted] are hydrogenated vegetable oils. While the excipient [redacted] is within the IIG limits, [redacted] is not listed in the IIG (1996). However, [redacted] has been used in approved application

(ANDA 73-507, miconazole nitrate vaginal Suppository) [redacted] mg/suppository). Since it is a hydrogenated vegetable oil, and in clinical study no side effects were noted, product should be safe.

COMMENTS

1. The firm should develop dissolution methods and specifications, submit the data to the agency at the earliest, and use them as quality control tool.

2. Summary report, IRB approval letter, drug composition, and product formulation data did not document the product Lot # used in the study. Lot # 0197-PB-13-A for test and Lot #11D317 for Ortho product were recorded only in the clinical report. In future, the firm should document the Lot # of the products adequately.

3. There are three evaluable parameters considered by the Medical Officer at FDA: clinical cure rate, mycological cure rate, and therapeutic cure rate. The medical and statistical evaluations indicate, that on the third visit, mycologic, clinical and therapeutic cure rates for G&W and Ortho miconazole nitrate vaginal suppositories are equivalent. The parameter values were obtained at second (V2) and third (V3) visits, and were statistically analyzed using 90% CI criteria.

RECOMMENDATION

The comparative clinical study conducted by G&W Laboratories, Inc., on its miconazole nitrate vaginal suppositories, 100 mg, Lot # 0197-PB-13-A, comparing it to Ortho's Monistat-7, 100 mg, Lot #11D317 has been found acceptable by the Division of Anti-Infective Drug Products, and by the Division of Bioequivalence. The study demonstrates that G&W Laboratories' miconazole nitrate vaginal suppository, 100 mg, is bioequivalent to the reference product, Monistat-7^{R}, 100 mg, manufactured by Ortho.

The firm should be informed of the comments #1-2 and the recommendation.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar

/S/ Date 1/30/1997

Table 1. Comparative Formulation

Ingredients	G&W Labs. mg/Suppository	Ortho USA mg/Suppository
Miconazole nitrate, USP	100	100
Hydrogenated Vegetable Oil	----	PNG[1]

[1] Potency Not Given

JAN 30 1996

Miconazole Nitrate
100 mg vaginal suppository
ANDA: 74-414
Reviewer: James D. Henderson
File: 74414S.093

G & W Laboratories
South Plainfield, NJ
Submitted:
October 8, 1993 &
May 12, 1995 &
September 5, 1995

REVIEW OF A BIOEQUIVALENCE STUDY: RESULTS OF A COMPARATIVE CLINICAL TRIAL

BACKGROUND:

1. The original submission was 10/8/93 and contained the results of a bioequivalence study conducted as a clinical trial comparing the test product miconazole nitrate 100 mg vaginal suppository (G & W) with the reference listed drug (RLD) Monistat-7® Vaginal Suppository 100 mg (RW Johnson, NDA #18-520, approved 3/15/82). The test product formulation is shown in Table 1.

2. On 11/16/93 OGD issued a refuse to file letter to the sponsor. On 12/6/93 the sponsor submitted an amendment responding to the requested information for filing, and filing was accepted on 12/7/93.

3. The clinical trial was initiated in 11/91 (Protocol #901287, conducted by _____ using the following biostudy products:

Test Product: miconazole nitrate vaginal suppository 100 mg, G & W lot #0197-PB-13-A, assay _____ manufactured 10/9/91; theoretical yield, _____ actual yield, _____

RLD: Monistat-7® Vaginal Tablet 100 mg, RW Johnson lot #11D-317 (exp 4/95), assay 97.7-98.6%

NOTE: In v. 1.1 the sponsor reported <u>two</u> assay results for each of the biostudy lots. If the lowest value for the lot of RLD (97.7%) is used, the potency difference from the test product lot is 5.1-5.4%. If average values are used, the difference in potency is 102.95% (test) minus 98.15% (RLD), or 4.8%.

4. Two amendments addressing bioequivalence issues have been submitted:

- The medical reviewer requested reformatted tables for the study data directly from the sponsor (telephone request). the sponsor submitted an amendment on 5/12/95.
- The sponsor submitted another amendment on 9/5/95 which also contained reformatted tabular data, also in response to a request from the medical reviewer.

CONSULT REVIEWS:

1. The study results were forwarded (10/22/93) to the Division of Anti-Infective Drug Products (HFD-520) for medical consultation review. The consultation review was completed 12/6/95 and is appended to this review.

2. Medical Review and Evaluation, Julius S. Piver, M.D., Medical Officer, DAIDP (HFD-520):

a. Conclusion

The results of these analyses fail to support the applicant's claim of therapeutic equivalence for its test product miconazole nitrate vaginal suppository 100 mg compared to the RLD Monistat-7® Vaginal Suppository 100 mg. The formulations of miconazole nitrate vaginal suppository 100 mg manufactured by G & W (test product) and RW Johnson (RLD) are not therapeutically equivalent for efficacy in the treatment of recurring vulvovaginal candidiasis.

b. Recommendation

From a clinical standpoint, the approval of G & W Laboratories' miconazole nitrate vaginal suppository 100 mg is not recommended for the treatment of vulvovaginal candidiasis.

c. Concurrences

Concurrence for this recommendation was given by Renata Albrecht, M.D., SMO, DAIDP (HFD-520) on 12/12/95, and by Mary Fanning, M.D., Ph.D., Director, DAIDP (HFD-520) on 12/18/95.

3. Statistical Review and Evaluation, Ralph Harkins, Ph.D., Group Leader, Group 7, Biometrics (HFD-713):

a. Reporting of Results

The Statistical Reviewer reported results for 90% confidence intervals (CI) as follows:

$$n_t, n_c \ (CI) \ p_t, p_c$$

where n_t and n_c are the sample sizes for the test product and RLD, respectively, and p_t and p_c are the success rates for the test product and RLD, respectively. The allowable difference is 20% for cure/failure type trials, and 20% of the active control mean response for other type of response variables. Since the generic product must not be either better than nor worse than the RLD, the 90% CI must be contained within the ± 20% difference. The equations used to compute the CI and the subsequent calculations were not included in the review.

b. Summary of Results: Mycological Cure Rates

- Visit 2: The data used by the Medical Officer (MO) result in a 90% confidence interval (CI) of $_{51,45}(-0.17,0.07)_{0.88,0.93}$. The G & W product is therapeutically equivalent to the RW Johnson product at this time point.

- Visit 3: The data used by the MO result in a 90% confidence interval (CI) of $_{51,45}(\mathbf{-0.23},0.07)_{0.76,0.84}$. The G & W product is slightly inferior to the RW Johnson product due to failure to meet the lower bound value of -0.20 at this time point.

c. Summary of Results: Clinical Cure Rates

- Visit 2: The data used by the MO result in a 90% confidence interval (CI) of $_{51,45}(\mathbf{-0.24},0.02)_{0.84,0.98}$. The G & W product is statistically inferior to the RW Johnson product at this time point.

- Visit 3: The data used by the MO result in a 90% confidence interval (CI) of $_{51,45}(-0.19,0.06)_{0.84,0.90}$. The G & W product is statistically equivalent to the RW Johnson product.

d. Summary of Results: Therapeutic Cure Rates

- Visit 3: The data used by the MO result in a 90% confidence interval (CI) of $_{51,45}(\mathbf{-0.30},0.03)_{0.69,0.82}$. The G & W product is possibly inferior to the RW Johnson product.

e. Conclusion

The results of statistical analyses fail to support G & W's claim that their formulation of miconazole nitrate vaginal suppository 100 mg is therapeutically equivalent to RW Johnson's Monistat-7® Vaginal Suppository.

4. The BE reviewer's recommendation is based on the conclusions of the MO and Statistician that the study fails to demonstrate therapeutic equivalence of the two formulations.

DEFICIENCIES:

1. The applicant's Visit 3 data for mycologic cure rates fails to support the claim of equivalency and the reviewing Medical Officer's data shows inequivalency due to failure to meet the lower bound of -0.20.

2. The applicant's Visit 2 data for clinical cure rates fails to support the claim of equivalency and the reviewing Medical Officer's data shows inequivalency due to failure to meet the lower bound of -0.20.

3. The applicant's Visit 3 data for therapeutic cure rate fails to support the claim of equivalency and the reviewing Medical Officer's data shows inequivalency due to failure to meet the lower bound of -0.20.

RECOMMENDATIONS:

1. The bioequivalence study conducted by G & W laboratories on its miconazole nitrate vaginal suppository 100 mg, lot #0197-PB-13-A, comparing it to Monistat-7® Vaginal Suppository 100 mg has been found unacceptable by the Division of Bioequivalence due to deficiencies 1-3.

2. The sponsor should be informed of deficiencies 1-3 and the recommendation.

/S/

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK /S/ 1/26/96

Concur: /S/ Date 1/30/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

JDH/gj/1-26-96/74414

cc: ANDA #74-414 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

Table 1 - Test Product Formulation

FOR INTERNAL USE ONLY

INGREDIENT	AMOUNT/TAB
miconazole nitrate, USP [redacted]	100.0 mg
[redacted]	[redacted]
[redacted]	[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

MEDICAL REVIEW

Attachment 1

Supervisory Medical Officer's
Consult Memorandum
ANDA 74-414

RAGI:
1. THIS IS EARLIER EVALUATION.
2. IT WAS CHANGED.
3. SEE ATTACHMENTS 7, 8 & 9

Date: 3 October, 1996

To: Director, Office of Generic Drugs
HFD-615

From: Brad Leissa, MD
Supervisory Medical Officer, DAIDP (HFD-520)

Through: David Feigal, MD, MPH
Acting Director, DAIDP (HFD-520)

RE: G&W Laboratories' miconazole nitrate 100 mg vaginal suppository ANDA

This application seeks ANDA approval for miconazole nitrate 100 mg vaginal suppositories in the treatment of women with vaginal candidiasis. The applicant submitted the data from a single study, #901287. &W Laboratories' generic product was compared to Ortho's Monistat-7 (miconazole) 100 mg vaginal insert in a multicenter, double-blind, randomized, parallel study. Patients self-administered the vaginal cream nightly for 7 consecutive days.

In the applicant's presentation of their analysis, patients were assessed at two posttreatment visits: Visit 2 (study days 14-17) and visit 3 (study days 35-42). By visit 3, the **therapeutic cure** rate (combined clinical and mycologic cures) was 39/55 (71%) for G&W Laboratories' miconazole nitrate 100 mg vaginal suppository vs. 38/54 (70%) for Ortho's active control. Using the 90% confidence interval approach (corrected), the upper and lower limits around the difference between both the two study arms are {-15.7%, +16.7%}.

In the medical officer's review of this ANDA, the evaluation period for these two windows were extended to allow for weekends and holidays: Visit 2 (study days 13-18) and visit 3 (study days 34-43). DAIDP considers visit 3 the test-of-cure visit. The therapeutic cure rate is used to evaluate overall efficacy.

According to the reviewer's reanalysis of the submitted data, at visit 3, the therapeutic cure rate was 38/55 (69%) for G&W Laboratories' miconazole nitrate 100 mg vaginal suppository vs. 41/53 (77%) for Ortho's active control. Based on the MO's reanalysis, using the 90% confidence interval approach (corrected), the upper and lower limits around the difference between the two study arms are {-24.1%, +7.5%}. From a statistical standpoint, because the lower limit exceeds -20%, the applicant has failed to demonstrate therapeutic equivalence to Ortho's Monistat-7 (miconazole) 100 mg vaginal insert.

Recommendation: This application is **not approvable**.

/s/

Brad Leissa, M.D.

CC: ANDA 74-414
HFD-630
HFD-340
HFD-520
HFD-520/SMO/BLeissa
HFD-520/Biostats/DLin
HFD-520/CSO/CChi

Concurrence Only:
HFD-520/DivDir/Feigal /s/ 10.9.96

Statistical Review and Evaluation
(Consult)

ANDA#: 74-414

OCT 4 1996

Applicant: G and W Laboratories, Inc..

Name of Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Documents Reviewed: Medical Officer's Review (5/23/96) submitted for Consult

Indication: Vaginal Candidiasis

Medical Input: Dr. Julius Piver, HFD-520

A. INTRODUCTION

This is a Generic Drug Product. Therefore, we use the 90% confidence interval (CI) for determining therapeutic and related equivalency statements. This is the same as using two one-sided 95% confidence intervals. The allowable confidence interval length in Generic Drug trials is 20% for cure/failure type trials and within 20% of the active control mean response for other type response variables. Since the concept is that the new agent is not to be either better than or worse than the control agent, the 90% CI must be completely contained within the -20% and +20% delta values.

Generic Drug Division trials of vaginal care products are generally standardized, therefore, a full statistical evaluation of the total submission is only done if problems in conduct or reporting of trial results are noted by the Reviewing Medical Officer (RMO). When there are no problems, our review is confined to check statistical results developed by the RMO or to compute confidence intervals on data as derived by the RMO. Since clinical trial data is not provided to the statistician, no evaluation of consistency among (between) investigators by treatment can be made. If the odds ratios differ significantly among the investigators, the following evaluation will not account for this.

B. CALCULATIONS AND EVALUATION

All calculations are based on data as supplied by the RMO. No effort has been made to check for internal consistency or to make other data validity checks. All confidence interval results are presented as two-sided 90% confidence intervals in the format $_{nt,\,nc}(CI)_{\,pt,\,pc}$, where n_t and p_t are respectively the sample size and success rates for the test agent (G&W's product - miconazole insert 100 mg) and n_c and p_c are similarly defined for the control agent (Ortho's product - Monistat-7 miconazole insert 100 mg).

Mycological and clinical response rates are secondary efficacy criteria and the therapeutic

response rate is the primary efficacy criterion.

The following CIs are based on the Sponsor's data. For clinical response at the first post-treatment visit (V2), comparing G&W (the sponsor's product) to Ortho yield the following 90% CI: $_{55,54}$ (-.163, .096)$_{.84,.87}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{49,51}$ (-.114, .069)$_{.94,.96}$. For mycological response at the first post-treatment visit (V2), the G&W versus Ortho 90% CI is $_{55,54}$ (-.157, .051)$_{.89,.94}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{49,51}$ (-.107, .174)$_{.86,.82}$.

For therapeutic response at second post-treatment visit (V3), the G&W versus Ortho 90% CI is $_{55,54}$ (-.156 .167)$_{.71,.70}$.

The following CIs are based on the Medical officer's data. For clinical response at the first post-treatment visit (V2), comparing G&W (the sponsor's product) to Ortho yield the following 90% CI: $_{55,53}$ (-.229, -.024)$_{.85,.98}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{55,53}$ (-.069, -.186)$_{.85,.92}$. For mycological response at the first post-treatment visit (V2), the G&W versus Ortho 90% CI is $_{55,53}$ (-.157, .053)$_{.89,.94}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{55,53}$ (-.178, .121)$_{.76,.79}$.

For therapeutic response at second post-treatment visit (V3), the G&W versus Ortho 90% CI is $_{55,53}$ (-.241 .075)$_{.69,.77}$.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The results of the analyses of data derived from the RMOs review fail to support the sponsor's claim that their formulation of Miconazole Nitrate Suppository, 100 mg is therapeutically equivalent to the active comparator agent.

/S/ 10/4/96

Daphne Lin, Ph.D.
Acting Team Leader, Biometrics IV

cc:
Orig. ANDA 74-414
HFD-520
HFD-520/Dr. Feigal
HFD-520/Dr. Leissa
HFD-520/Dr. Chi
HFD-630/Ms. Parise
HFD-725/Dr. Harkins
HFD-725/Dr. Lin
Chron.
This review contains 2 pages.

Attachment- 1

Supervisory Medical Officer's
Consult Memorandum
ANDA 74-414

RABI:

1. THIS IS EARLIER EVALUATION.
2. IT WAS CHANGED.
3. SEE ATTACHMENTS 7, 8 & 9

Date: 3 October, 1996

To: Director, Office of Generic Drugs
HFD-615

From: Brad Leissa, MD
Supervisory Medical Officer, DAIDP (HFD-520)

Through: David Feigal, MD, MPH
Acting Director, DAIDP (HFD-520)

RE: G&W Laboratories' miconazole nitrate 100 mg vaginal suppository ANDA

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In the applicant's presentation of their analysis, patients were assessed at two posttreatment visits: Visit 2 (study days 14-17) and visit 3 (study days 35-42). By visit 3, the **therapeutic cure** rate (combined clinical and mycologic cures) was 39/55 (71%) for G&W Laboratories' miconazole nitrate 100 mg vaginal suppository vs. 38/54 (70%) for Ortho's active control. Using the 90% confidence interval approach (corrected), the upper and lower limits around the difference between both the two study arms are {-15.7%, +16.7%}.

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Recommendation: This application is **not approvable**.

/S/

Brad Leissa, M.D.

CC: ANDA 74-414
HFD-630
HFD-340
HFD-520
HFD-520/SMO/BLeissa
HFD-520/Biostats/DLin
HFD-520/CSO/CChi

Concurrence Only:
HFD-520/DivDir/Feigal /S/ 10.9.96

ANDA 74-414

DATE SUBMITTED:	OCTOBER 8, 1993
DATE RECEIVED:	OCTOBER 22, 1993
DATE OF AMENDMENT:	JANUARY 4, 1995
DATE OF AMENDMENT:	MAY 16, 1996
DATE COMPLETED:	MAY 23, 1996

MEDICAL CONSULTATION FROM HFD-520
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Requested By: Office of Generic Drugs
HFD-615

Applicant: G&W Laboratories, Inc.
111 Coolidge Street
South Plainfield, New Jersey 07080

Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Drug Category: Anti-fungal

Dose Form: Vaginal suppository

Dosage: One 100mg suppository inserted into the vagina nightly for seven consecutive nights (Day 1 start).

Purpose:

The purpose of this ANDA is to obtain market approval comparable to the innovator product of a generic form of miconazole 100mg vaginal insert manufactured by G&W Laboratories, Inc. for the treatment of vaginal candidiasis.
The Applicant has conducted a study comparing the efficacy and safety of miconazole 100mg vaginal insert by G&W and Monistat-7 100mg vaginal insert (Ortho) in the treatment of women with vaginal candidiasis.

In the United States, vulvovaginal candidiasis continues to be one of the most frequently recurring vaginal infections diagnosed in our female population of all ages. Since the 1970's, candidiasis has been safely and effectively treated by the polyenes (e.g., nystatin) and imidazoles (e.g., clotrimazole, miconazole). Miconazole is a synthetic imidazole-derivative antifungal agent that is fungicidal in vitro against species of the genus Candida. It is clinically indicatd for the local treatment of vulvovaginal candidiasis and since 1990 has been available as an over-the-counter seven day treatment regimen. The Applicant desires to make available to the consumer its miconazole 100 mg vaginal insert which they believe to be comparable in safety and efficacy to the presently marketed Monistat-7 (Ortho) 100 mg suppository.

Comparison of Miconazole 100m Suppositories (G&W) and Monistat-7 (Ortho) In the Treatment of Vulvovaginal Candidiasis

(Study # 901287)

Study Design:

The study was a multiple dose, multi-center, double-blind, randomized, parallel comparison of miconazole insert 100 mg (G&W) to Monistat-7 miconazole insert 100 mg (Ortho). Patients with clinically-suspected vaginal candidiasis were randomly assigned to one of two treatment groups who were recruited by 9 qualified gynecologists and 5 qualified general practitioners.
A KOH smear and mycologic culture were performed on the vaginal discharge from each patient at the time of the initial visit and at each of two follow-up visits. The patients were seen for a total of three visits -- entry (baseline), first post-treatment visit (V2), and second post-treatment visit (V3).

Monitoring: The study was conducted in accordance with the "Guidelines on Research Involving Human Subjects" (Medical Research Council of Canada,1987). Regular monitoring visits were made to each study center during the study by _____ who established that the protocol was being followed and that data were being collected accurately. At the conclusion of the study unused study medications were retained and stored with permanent study files by _____ There was no mention in the data as to whether or not all evaluable patients took the full course of therapy. It can reasonably be concluded that they did, in the absence of data to the contrary based on the above monitoring.

There were fourteen investigators from Quebec and Ontario, Canada (see above) who enrolled a total of 168 patients into the study. They were responsible to the _____ for the recruitment of patients to participate in the studies that were conducted for this ANDA.

ENTRY (BASELINE) VISIT:

A history and physical examination were performed to establish the patient's eligibility for the study.
Inclusion Criteria: patients who were otherwise healthy females with clinical signs and symptoms of vaginitis (itching, burning/irritation, vulvar erythema, edema or excoriations and/or vaginal erythema or edema) and positive KOH and culture for *Candida albicans* were entered into the study. To be included in the study patients had to fulfill these inclusion criteria:

* Informed written consent of the patient: patients were entered into the study only after reading, understanding, and signing an informed consent. Patients were supplied with the name and telephone number of the physician to call in the event of an adverse reaction.

* Positive KOH smear and culture for *Candida albicans* within one week of start of treatment.

* Age ≥ 18 years.

* Patients must not be expected to begin menses during the treatment period. KOH and culture were repeated if treatment start was delayed more than 7 days

* Sexually active patients must be using a reliable method of birth control (oral contraceptives, diaphragm with spermicide, etc.)

* Patients must agree to abstain from douches, tub baths, swimming, sexual intercourse and other activities likely to alter the disposition of drug in the vagina during treatment.

* Sexual intercourse following the treatment period must involve the use of a condom.

Exclusion Criteria:

The presence of any of the following excluded a patient from participation:

- recurring vaginal infections known to be resistant to standard treatment
- pregnancy or lactation; urine pregnancy test will be carried out at study entry
- coexisting sexually transmitted disease
- known sensitivity to imidazole antifungal agents
- any significant chronic illness
- patients with symptoms of infection other than *Candida*
- non-compliant behavior
- use of any systemic anti-infectives, anti-mycotics, corticosteroids or immunosuppressive drugs within 7 days entry into the study
- use of any vaginal douches or feminine sprays within the 48 hours preceding study entry
- any anatomical anomaly likely to affect therapeutic efficacy of the test medications.

rocedures

Once the patient signed the informed consent form and it was determined that she qualified for enrollment in the study, the following took place:

* Randomization Procedures:

  Each patient was assigned a sequential number to which one of the treatments was randomly assigned.

* Drug Administration:

  Patients were instructed to insert one tablet of the assigned vaginal tablet formulation into the vagina each evening at bedtime for seven consecutive nights, starting at Day 1. All study tablets were supplied in boxes of seven tablets packaged such that the patient was not able to identify the brand of the particular treatment assigned.

* Clinical Determinations:

  Evaluations of the affected area were made at the preliminary visit to establish a baseline. The parameters evaluated were erythema, discharge, itching (pruritus) and burning. The severity of each parameter was evaluated on a scale of 0-3 with 0=absent, 1=mild, 2=moderate, 3=severe. Total clinical response was determined for each patient as mild, moderate, or severe by the Physician's Clinical Evaluation.

  To be enrolled, the patient had to have clinical evidence of candida vaginitis, as characterized by the presence of the above signs and symptoms.

* Microbiological Determinations:

  KOH smear of the infected area; specimens were taken from an area of active lesion and a KOH prep made.

  Mycological culture of infected area; specimens were cultured on an appropriate culture medium and incubated at 37oC.

  Patients were to be KOH and culture positive to be enrolled in the study.

* Before distribution to the investigators the medication was labeled in such a way that the origin of the products could not be identified. The test and reference medications were then re-packed into identical boxes, each containing 7 strip packed tablets. The boxes were sealed so that the investigators did not see or handle the medication.

* At the conclusion of the study, unused study medications were retained by _____ and stored with permanent study files.

* Patient Instructions:

Patients were asked to complete a daily diary to record clinical symptoms by severity from Day 1 of treatment until Visit 3 (i.e. approximately 30 days after completion of treatment). The diaries were used to evaluate the onset of action and degree of clinical efficacy of the assigned medication.

FIRST FOLLOW-UP VISIT: (Post treatment days 7-10=Visit 2)

Patients were told to return for follow-up visits 7 days after completion of the 7 day treatment regimen. At that time they were evaluated clinically and microscopically by KOH smear and fungal culture.

SECOND FOLLOW-UP VISIT: (Post treatment days 28-35=Visit3)

Patients were told to return for the second follow-up visits 30 days post-treatment. At that time they had a clinical examination and were evaluated microscopically by KOH and fungal culture, and evaluated for possible side effects.

Patients were instructed to return study medication at this re-visit, and were questioned by the investigator concerning possible adverse drug effects.

Procedures at the second follow-up visit were identical to those of the first follow-up visit.

Any adverse reactions experienced by the patient, or noted by the investigating physician, were reported on an adverse event form. These will be described in detail later in this report. The patients were also advised to record the severity of itching or burning daily from Day 1 until 30 days after completion of treatment. Concomitant medications could be used as required, provided neither the condition being treated nor the medication being taken affected the progression of the vaginal infection or therapeutic effects of the treatment.

Patients were fully informed regarding all aspects of the trial including potential side effects of the study medication.

Evaluation of Efficacy Outcome

The applicant evaluated the efficacy of the product at both the first post-treatment and the second post-treatment visits by examination of the patient for signs and symptoms and by taking KOH prep and culture samples and recording the findings according to the above scoring system (see page 5) as well as the result of the prep and culture.

The Applicant defined the population enrolled as those women who were randomized to treatment, and the "eligible" population as those patients who met all inclusion and exclusion criteria at entry.

In addition to meeting inclusion and exclusion criteria, additional evaluability criteria included:

* Patient agreed to restrictions in protocol.
* Return for both followup visits within the established windows.
* Culture and KOH results at both followup visits.
* Patient was a normal, healthy female.
* Patient $\geq$ 18 years of age, weighing $\geq$ 45kg, and within 20% of her ideal weight.
* Patient exhibited signs and symptoms of vaginal candidiasis

FIRST POST-TREATMENT VISIT:

Visit 2 (Day 14 of study - 7 days post-treatment - a window of 14-17 days was accepted)by the Applicant:

To be considered evaluable for the first post-treatment visit, patients had to have met all inclusion and exclusion criteria, and had to return for the first post-treatment visit within the 7-10 day post-treatment window. The reviewing Medical Officer had to exclude more patients than the Applicant since patients returned for assessment outside of this window. A wider window of 13-18 days was accepted by the M.O. to allow for weekends/holidays.

Patients were examined by their physician and the degree of clinical symptoms and lesions was recorded. KOH prep and culture samples were taken for evaluation of mycologic cure. The mycological cure rate was the primary efficacy parameter. Patients found to have positive KOH or culture were recorded as "treatment failure" and did not need to return for visit 3.

Clinical Efficacy and Mycological Efficacy:

CLINICAL OUTCOME:

CURE----------resolution of all signs & symptoms of disease
IMPROVEMENT-----significant amelioration of signs & symptoms of disease
FAILURE---------persistence of signs & symptoms of disease

MYCOLOGICAL OUTCOME:

ERADICATION-----negative KOH and negative fungal culture
PERSISTENCE-----positive KOH and/or positive fungal culture

SECOND POST-TREATMENT VISIT:

Visit 3 (Day 37 of study - 30 days post-treatment - a window of 35-42 days was acceptedby the Applicant:

To be considered evaluable for the second post-treatment visit, patients had to have met all inclusion and exclusion criteria, and had to return for the second post-treatment visit within the 28-35 day post-treatment window. The reviewing Medical Officer had to exclude more patients than the Applicant since patients returned for assessment outside of this window. A wider window of 27-36 days was accepted by the M.O. to allow for weekends/holidays.

Within 28-35 days after completion of the 7 day treatment regimen, patients were re-evaluated for signs and symptoms. KOH prep and culture samples were repeated for evaluation of mycological cure. Patients were evaluated for clinical efficacy, for mycological efficacy and for therapeutic outcome.

CLINICAL OUTCOME:

CURE----------resolution of all signs and symptoms of disease

IMPROVEMENT-----significant amelioration of signs and symptoms of disease

FAILURE---------persistence of signs and symptoms of disease

COMMENT: The reviewer only accepted categories of CURE *(resolution of all signs and symptoms) or* FAILURE *(persistence of any sign or symptom of disease) at the second post-treatment visit.*

MYCOLOGICAL OUTCOME:

ERADICATION-----negative KOH and negative fungal culture

PERSISTENCE-----positive KOH and/or positive fungal culture

THERAPEUTIC OUTCOME:

CURE----------resolution of all signs and symptoms of disease at the second post-treatment visit (patients had to be considered either a cure or an improvement at the first post-treatment visit also) and have negative KOH and fungal culture results at all followup visits.

FAILURE---------persistence of signs and symptoms of disease or positive KOH and/or fungal culture.

COMMENT: The reviewer considered only patients who had resolution of all signs and symptoms of disease at the second post-treatment visit (and patients had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture results at all visits to be THERAPEUTIC CURES.

Patients who were either a clinical failure and/or a mycological failure at either of the two follow-up visits were considered to be THERAPEUTIC FAILURES.

ESULTS:

A total of fourteen investigators (9 gynecologists and 5 general practitioners) enrolled a total of 168 patients of whom 84 were randomized to the G&W 100mg vaginal insert and 84 were randomized to the Ortho Monistat-7 100mg insert. They were responsible to the [redacted] for the recruitment of patients to participate in the studies that were conducted for this ANDA. The curriculum vitae of each of the investigators was carefully reviewed and each was found to be qualified to conduct the study. The investigator, the geographical location of the investigator, and the number of patients enrolled for each investigator are listed in Table 1 below.

According to the Applicant, 109 patients were eligible for efficacy evaluation (See Table 5).

Table 1
Patients Evaluable by Applicant G&W by 1st Follow-up Visit

Investigator/Location	Patients Given Miconazole (G&W)	Patients Given Monistat-7	Total
[redacted]	5/8	3/8	8/16 (50%)
	2/8	5/8	7/16 (44%)
	0/5	0/5	0/10 (0%)
	6/6	3/4	9/10 (90%)
	9/11	7/12	16/23 (69%)
	8/9	11/13	19/22 (86%)
	0/1	0/0	0/1 (0%)
	12/12	11/12	23/24 (96%)
	0/2	0/1	0/3 (0%)
	9/12	9/12	18/24 (75%)
	3/7	4/4	7/11 (64%)
	0/0	1/2	1/2 (50%)
	1/1	0/1	1/2 (50%)
	0/2	0/2	0/4 (0%)
	55/84 (66%)	54/84 (64%)	109/168 (65%)

Table 2

Exclusion From Efficacy Analysis
By Applicant G&W N = 59

Reason	Code	G&W	Ortho	Total
Lost to follow-up or missing data				
Came for visit 1 only	(2a)	1	3	4
Came for visit 1 & 2 only	(2b)	2	0	2
Missing KOH/culture @ any visit	(2c)	4	5	9
Returned outside of follow-up Window for visit 2 or visit 3	(2d)	5	4	9
Protocol violation (Not specified by Applicant)	(3a)	4	7	11
Negative culture on admission	(3c)	12	11	23
Drop out for ADR	(5)	1	0	1
TOTAL		29	30	59

Table 3

Ineligible for Efficacy Analysis N = 59

Investigator	Patient Number	G&W/Ortho	Reason
1. [redacted]	# 02	Ortho	3c
2. [redacted]	# 06	G&W	2d
3. [redacted]	# 11	G&W	3c
4. [redacted]	# 12	G&W	2c
5. [redacted]	# 13	Ortho	3c
6. [redacted]	# 16	G&W	2a
7. [redacted]	# 17	G&W	3a
8. [redacted]	# 18	Ortho	2c
9. [redacted]	# 19	G&W	3c
10. [redacted]	# 20	Ortho	3c
11. [redacted]	# 25	Ortho	3a
12. [redacted]	# 38	Ortho	2c
13. [redacted]	# 44	Ortho	3a
14. [redacted]	# 50	Ortho	3a

TABLE 3 - Continued

Investigator	Patient Number	G&W/Ortho	Reason
15. [redacted]	# 54	G&W	3a
16. "	# 58	G&W	2c
17. "	# 60	G&W	3a
18. "	# 62	Ortho	2a
19. [redacted]	# 65	G&W	3a
20. "	# 67	G&W	3c
21. "	# 69	Ortho	3c
22. "	# 71	G&W	3c
23. "	# 72	Ortho	3a
24. "	# 74	G&W	3c
25. "	# 77	Ortho	3c
26. "	# 78	G&W	2c
27. "	# 80	G&W	3c
28. [redacted]	# 90	G&W	2d
29. "	# 92	G&W	2d
30. "	# 94	G&W	3c
31. [redacted]	# 96	Ortho	2a
32. [redacted]	# 98	Ortho	3c
33. "	# 100	G&W	3c
34. "	# 101	Ortho	3c
35. "	# 104	G&W	3c
36. "	# 105	Ortho	2d
37. "	# 108	Ortho	2d
38. "	# 109	Ortho	2c
39. "	# 110	G&W	2d
40. [redacted]	# 113	G&W	3c
41. [redacted]	# 115	Ortho	3a
42. "	# 120	Ortho	2a
43. "	# 121	Ortho	3a
44. "	# 122	Ortho	3a
45. "	# 123	G&W	5
46. "	# 128	G&W	2d
47. [redacted]	# 129	G&W	2b
48. "	# 130	Ortho	2c
49. "	# 131	Ortho	3c
50. "	# 132	G&W	3c
51. "	# 133	Ortho	3c
52. "	# 134	Ortho	3c
53. "	# 135	G&W	2b
54. "	# 136	G&W	3c
55. "	# 137	G&W	2c
56. "	# 138	Ortho	2c
57. [redacted]	# 143	Ortho	2d
58. [redacted]	# 159	Ortho	2d
59. [redacted]	# 166	Ortho	3c

Table 4

Exclusion From Efficacy Analysis
By Investigator

Investigator (# enrolled)	Patients Given Miconazole G&W N = 84	Patients Given Monistat-7 Ortho N = 84	Total
[redacted] (16)	3	5	8
[redacted] (16)	6	3	9
[redacted] (10)	5	5	10
[redacted] e (10)	0	1	1
[redacted] (23)	2	5	7
[redacted] (22)	1	2	3
[redacted] (01)	1	0	1
[redacted] (24)	0	1	1
[redacted] (03)	2	1	3
[redacted] (24)	3	3	6
[redacted] (11)	4	0	4
[redacted] (02)	0	1	1
[redacted] (02)	0	1	1
[redacted] (04)	2	2	4
TOTAL (168)	29/84 (35%)	30/84 (36%)	59/168 (35%)

168 patients were enrolled in the study. 84 were in the G&W arm and 84 in the Ortho arm of the study. 29 patients were excluded by the Applicant from the G&W arm and 30 were excluded by the Applicant from the Ortho arm. See Table 3. There were 109 patients remaining evaluable, 55 in the G&W arm and 54 in the Ortho arm.

The total number of patients evaluable by the Applicant was ~~109~~ 55 patients in the G&W group and 44 patients in the Ortho group. The reviewing Medical Officer determined that there were 108 patients evaluable, excluding one patient from the Ortho group for returning outside the accepted window for visit 3. This was patient # 75 enrolled by ———— in the Ortho arm of the study. Thus 31 patients out of the 84 enrolled given Monistat-7 were excluded from analysis by the M.O. instead of the 30 patients excluded by the Applicant. The Applicant and the M.O. excluded 29 patients from the G&W arm of the study from efficacy analysis.

Table 5

Demographic Data

	Observed	Minimum-Maximum	Mean
G&W	**N = 55**	Ht (cm) 128-173 (51-68")	162 (63")
		Wt (kg) 46-93 (99-204#)	60 (132#)
		Age (yr) 16-52 (16-52yr)	31 (31yr)
Ortho	**N = 54**	Ht (cm) 150-177 (59-66")	162 (63")
		Wt (kg) 39-121 (86-266#)	63 (138#)
		Age (yr) 18-64 (18-64yr)	32 (32yr)

According to the Applicant, there was no statistically significant difference between the two groups in age, height, and weight.

The applicant did not classify the patients by race.

CLINICAL OUTCOME - PER APPLICANT

Table 6

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	49/55 (89%)	42/49 (86%)
Ortho	51/54 (94%)	42/51 (82%)

Table 6a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	46/55 (84%)	46/49 (94%)
Ortho	47/54 (87%)	49/51 (96%)

Table 6b

Therapeutic Cure Rate

Treatment Group	Visit 3
G&W	39/55 (71%)
Ortho	38/54 (70%)

Mycological cure was defined as KOH and culture results negative at both return visits 2 and 3. **Clinical cure** was defined as an improvement in symptoms at visit 2 as compared to visit 1 **and** absence of symptoms at visit 3. **Therapeutic cure** was defined as resolution of **all** signs and symptoms at visit 3 and negative KOH and fungal culture results at visit 2 and visit 3.

CLINICAL OUTCOME - PER MEDICAL OFFICER

Table 7
Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	49/55 (89%)	42/55 (76%)
Ortho	50/53 (94%)	42/53 (79%)

Table 7a
Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	47/55 (85%)	47/55 (85%)
Ortho	52/53 (98%)	49/53 (92%)

Table 7b
Therapeutic Cure Rate

Treatment Group	Visit 3
G&W	38/55 (69%)
Ortho	41/53 (77%)

Mycological cure was defined as KOH and culture results negative at both return visits 2 and 3. **Clinical cure** was defined as an improvement in symptoms at visit 2 as compared to visit 1 **and** absence of symptoms at visit 3. **Therapeutic cure** was defined as resolution of **all** signs and symptoms at visit 3 and negative KOH and fungal culture results at visit 2 and visit 3.

CLINICAL OUTCOME SUMMARY

At visit 2, the Applicant demonstrated an 89% mycological cure rate for the G&W product and a 94% mycological cure rate for the Ortho product. The Medical Officer found similar results of 89% (G&W) and 94% (Ortho). At visit 3, the Applicant showed an 86% mycological cure rate for the G&W product and an 82% mycological cure rate for the Ortho product. The Medical Officer's review found results of 76% (G&W) and 79% (Ortho) mycological cure rates. It remains for statistical analysis to determine if the differences are significant.

The clinical cure rate at visit 2 per the Applicant was 84% for the G&W product and 87% for the Ortho product. The Medical Officer's review determined clinical cure rates at visit 2 of 85% (G&W) and 98% (Ortho). At visit 3, the Applicant found a clinical cure rate of 94% for the G&W product and 96% for the Ortho product. The Medical Officer determined clinical cure rates at visit 3 of 85% (G&W) and 92% (Ortho).

The therapeutic cure rate for the G&W group of patients was 71% per the Applicant and 70% for the Ortho patients. The Medical Officer's review determined a therapeutic cure rate of 69% for the G&W group and 77% for the Ortho group of patients. Statistical analysis is necessary to determine if that difference is significant.

Note: The denominators for visit 3 in Tables 6 and 6a differ from the denominators in Table 6b per the Applicant. Data from patients who were treatment failures at Visit 2 were excluded from Visit 3 analyses although included in overall calculations of cure, per the Applicant. This was discussed with the SMO who concurred with its incorrectness.

The therapeutic cure rate is the test-of-cure outcome parameter and the basis for approvability of all drugs for vaginal candidiasis.

Statistical analysis of the above information is necessary to determine if these figures fall within the 90% confidence interval of +/- 20% for approval.

SAFETY ANALYSIS

A total of 17 patients reported 23 adverse events according to the Applicant. There were 17 events in the G&W group and 6 events in the Ortho group. One patient (#123 G&W) discontinued the study due to nausea, headache and vaginal burning. It was uncertain if this adverse event was due to the study medication. None of the remaining reported events was unusual, considered serious, or definitely related to the study medication.

Table 8
Adverse Events

Treatment Group	Pt. #	Description	Visit	Related to Medication
G&W	# 12	Upper respiratory infection	3	NO
G&W	# 14	External irritation	2	Uncertain
G&W	# 21	Mild transient itching twice;	2	NO
		irritation > colonoscopy	3	NO
G&W	# 29	Mild transient nausea, mild intermittent burning	2	NO
G&W	# 43	Light abd. pain for 7 days at beginning of treatment	2	Uncertain
G&W	# 45	Abd. pain 10 min. after application of suppository	2	Uncertain
G&W	#123	Nausea, headache, vaginal burning; had to stop on 5th day of treatment	2	Uncertain
G&W	#141	External irritation	2	NO
G&W	#147	Allergic reaction, facial pruritus, history of prior allergic reactions to many factors	2	NO
G&W	#165	Pruritus 3 times daily for	2	Uncertain
		3 days	3	Uncertain
G&W	#167	Pruritus	2	NO
Ortho	# 10	Burning after intercourse	2	Uncertain
Ortho	# 15	Spotting; not menses	2	Uncertain
Ortho	# 28	Pelvic pain	3	NO
Ortho	# 32	Persistent irritation>treatment	2	Uncertain
		?allergy to capsule cover	3	Uncertain
Ortho	#144	Intermittent vulvar itching	2,3	NO
Ortho	#164	Pruritus and burning	2,3	NO

SUMMARY:

The Applicant, G&W Laboratories, Inc. has submitted data from a multi-center, study conducted by [redacted] Of Canada which compares two formulations of miconazole nitrate vaginal suppositories, 100 mg, manufactured by the Applicant, G&W and by Ortho Pharmaceuticals Inc (Monistat-7) in treating patients with vulvovaginal candidiasis. Based on these data, the Applicant is requesting approval of its miconazole 100 mg suppository for the seven day treatment of vulvovaginal candidiasis.

The criterion for demonstrating therapeutic equivalence for generic drugs is that the lower and upper limits of the 90% confidence interval around the difference between the two active products must lie within the interval (-.20, +.20).

The data that have been submitted by G&W Laboratories, Inc. have been verified an analyzed by me with statistical consultation from Ralph Harkins, Ph.D. of the Division of Biometrics. Statistical analysis is necessary to determine whether these data fall within the 90% confidence interval of +/- 20% for approval. If the statistical analysis substantiates the Applicant's claim of bioequivalency between the G&W product and the Ortho product on mycological, clinical and therapeutic grounds, it is my recommendation that approval be granted to G&W Laboratories, Inc. for its miconazole 100 mg vaginal insert for the treatment of vulvovaginal candidiasis.

CONCLUSION:

On the basis of my review of the data submitted with this ANDA, it is my conclusion that the formulations of miconazole 100 mg vaginal suppository manufactured by the Applicant, G&W Laboratories, Inc and by Ortho Pharmaceuticals, Inc. (Monistat-7) are clinically equivalent for safety and efficacy in the treatment of vulvovaginal candidiasis for seven days.

RECOMMENDATIONS:

If my conclusion is substantiated by statistical analysis, it is my recommendation that approval be granted to the G&W Laboratories, Inc. for its formulation of miconazole 100 mg vaginal suppository for the treatment of vulvovaginal candidiasis.

Labeling should be negotiated by the Office of Generic Drugs.

/S/

Julius S. Piver, M.D.
Medical Officer, (Ob-Gyn)

Concurrence
HFD/520/Dir/~~MFanning~~ /S/
HFD/520/SMO/BLeissa BL 10/3/95

ANDA 74-414

DATE SUBMITTED: October 8, 1993
DATE RECEIVED: October 22, 1993
DATE OF AMENDMENT: January 4, 1995
DATE COMPLETED: December 6 1995

Amend 1 6/27/95

MEDICAL CONSULTATION FROM HFD-520
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Requested By: Division of Generic Drugs
HFD-630

Applicant: G&W Laboratories, Inc.
111 Coolidge Street
South Plainfield, New Jersey 07080

Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Drug Category: Anti-fungal

Dose Form: Vaginal suppository

Dosage: One 100mg suppository inserted into the vagina nightly for seven consecutive nights (Day 1 start).

Purpose:

The purpose of this ANDA is to obtain market approval comparable to the innovator product of a generic form of miconazole 100mg vaginal insert manufactured by G&W Laboratories, Inc. for the treatment of recurrent vaginal candidiasis.
The Applicant has conducted a study comparing the efficacy and safety of miconazole 100mg vaginal insert by G&W and Monistat-7 100mg vaginal insert (Ortho) in the treatment of women with Candida.

Background:

In the United States, candidiasis continues to be one of the most frequent recurring vaginal infections diagnosed in our female population of all ages. Since the 1970's, Candidiasis has been safely and effectively treated by the polyenes (e.g., nystatin) and imidazoles (e.g., clotrimazole, miconazole). Miconazole is a synthetic imidazole-derivative antifungal agent that is fungicidal in vitro against species of the genus Candida. It is clinically indicated for the local treatment of vulvovaginal candidiasis and since 1990 has been available as an over-the-counter seven day treatment regimen. The Applicant desires to make available to the consumer its miconazole 100mg vaginal insert which they believe to be comparable in safety and efficacy to the presently marketed Monistat-7 (Ortho) 100mg suppository.

Study Design:

The study was a double blind, randomized (1:1), parallel group study comparing miconazole insert 100mg (G&W) to Monistat-7 miconazole insert 100mg (Ortho). Patients with clinically suspected candida vaginitis were randomly assigned to one of two treatment groups. A KOH smear and mycologic culture were performed on the vaginal discharge from each patient at the time of the initial visit and at each of two follow-up visits. The patients were seen for a total of three visits -- entry (baseline), first post-treatment visit (V2), and second post-treatment visit (V3).

Monitoring: The study was conducted in accordance with the "Guidelines on Research Involving Human Subjects" (Medical Research Council of Canada,1987). Regular monitoring visits were made to each study center during the study by [redacted] who established that the protocol was being followed and that data were being collected accurately. At the conclusion of the study unused study medications were retained and stored with permanent study files by [redacted] There was no mention in the data as to whether or not all evaluable patients took the full course of therapy. It can reasonably be concluded that they did, in the absence of data to the contrary based on the above monitoring.

Comparison of Miconazole 100mg Suppositories (G&W) and Monistat-7 (Ortho) In The Treatment of Vulvovaginal Candidiasis

ENTRY (BASELINE) VISIT:

A history and physical examination were performed to establish the patient's eligibility for the study.

Inclusion Criteria: patients who were otherwise healthy females with clinical signs and symptoms of vaginitis and positive KOH and culture for *Candida albicans* within one week of start of treatment were entered into the study. To be included in the study patients had to fulfill these inclusion criteria:

* Informed written consent of the patient: patients were entered into the study only after reading, understanding, and signing an informed consent. Patients were supplied with the name and telephone number of the physician to call in the event of an adverse reaction.

* Patients must not be expected to begin menses during the treatment period. KOH and culture were repeated if treatment start was delayed more than 7 days.

* Sexually active patients must be using a reliable method of birth control (oral contraceptives, diaphram with spermicide etc.)

* Patients must agree to abstain from douches, tub baths, swimming, sexual intercourse and other activities likely to alter the disposition of drug in the vagina during treatment.

* Sexual intercourse following the treatment period must involve the use of a condom.

* Clinical Determinations:

Evaluations of the affected area were made at the preliminary visit to establish a baseline. The parameters evaluated were erythema, discharge, itching (pruritus), and burning. The severity of each parameter was evaluated on a scale of 0-3 with 0=absent, 1=mild, 2=moderate, 3=severe. Total clinical response was determined for each patient as mild, moderate or severe by the Physician's Clinical Evaluation.

To be enrolled, the patient had to have clinical evidence of candida vaginitis, as characterized by the presence of the above signs and symptoms.

* Microbiological Determinations:

KOH smear of the infected area: Specimens were taken from an area of active lesion and a KOH prep made.

Mycologic culture of infected areas: Specimens were cultured on an appropriate culture medium and incubated at 37oC.

Patients were to be KOH and culture positive to be enrolled in the study.

Exclusion Criteria:

The presence of any of the following excluded a patient from participation:

- recurring vaginal infections known to be resistant to standard treatment
- pregnancy or lactation; urine pregnancy test will be carried out at study entry
- coexisting sexually transmitted disease
- known sensitivity to imidazole antifungal agents
- any significant chronic illness
- patients with symptoms of infection other than *Candida*
- non-compliant behavior
- use of any systemic anti-infectives, anti-mycotics, corticosteroids or immunosuppressive drugs within 7 days entry into the study
- use of any vaginal douches or feminine sprays within the 48 hours preceding study entry
- any anatomical anomaly likely to affect therapeutic efficacy of the test medications.

Procedures

Once the patient signed the informed consent form and it was determined that she qualified for enrollment in the study, the following took place:

* Randomization Procedures:

  Each patient was assigned a sequential number to which one of the treatments was randomly assigned.

* Drug Administration:

  Patients were instructed to insert one tablet of the assigned vaginal tablet formulation into the vagina each evening at bedtime for seven consecutive nights, starting at Day 1. All study tablets were supplied in boxes of seven tablets packaged such that the patient was not able to identify the brand of the particular treatment assigned.

* Before distribution to the investigators the medication was labeled in such a way that the origin of the products could not be identified. The test and reference medications were then re-packed into identical boxes, each containing 7 strip packed tablets. The boxes were sealed so that the investigators did not see or handle the medication.

* At the conclusion of the study, unused study medications were retained by [redacted] and stored with permanent study files.

* Patient Instructions:

  Patients were asked to complete a daily diary to record clinical symptoms by severity from Day 1 of treatment until Visit 3 (i.e. approximately 30 days after completion of treatment). The diaries were used to evaluate the onset of action and degree of clinical efficacy of the assigned medication.

FIRST FOLLOW-UP VISIT: (Post treatment days 7-10=Visit 2)

Patients were told to return for follow-up visits 7 days after completion of the 7 day treatment regimen. At that time they were evaluated clinically and microscopically by KOH smear and fungal culture.

SECOND FOLLOW-UP VISIT: (Post treatment days 28-35=Visit3)

Patients were told to return for the second follow-up visits 30 days post-treatment. At that time they had a clinical examination and were evaluated microscopically by KOH and fungal culture, and evaluated for possible side effects.

Patients were instructed to return study medication at this re-visit, and were questioned by the investigator concerning possible adverse drug effects.

Procedures at the second follow-up visit were identical to those of the first follow-up visit.

Evaluation of Efficacy Outcome

The Applicant evaluated the efficacy of the product at both the first post-treatment and the second post-treatment visits by examination of the patient for signs and sympmtoms and by taking KOH prep and culture samples and recording the findings according to the above scoring system (see Page 4) as well as the result of the prep and culture.

The Applicant defined the population enrolled as those women who were randomized to treatment, and the "eligible" population as those patients who met all inclusion and exclusion criteria at entry.

FIRST POST-TREATMENT VISIT:

Visit 2 (Day 14 of study - 7 days post-treatment - a window of 14-17 days was accepted):

To be considered evaluable for the first post-treatment visit, patients had to have met all inclusion and exclusion criteria, and had to return for the first post-treatment visit within the 7-10 day post-treatment window. The reviewing Medical Officer had to exclude more patients than the Applicant due to the larger window of return. A wider window was accepted to allow for weekends and holidays.

Patients were examined by their physician and the degree of clinical symptoms and lesions was recorded. KOH prep and culture samples were taken for evaluation of mycologic cure. The mycological cure rate was the primary efficacy parameter. Patients found to have positive KOH or culture were recorded as "treatment failure" and did not need to return for visit 3.

Clinical Efficacy and Mycological Efficacy:

CLINICAL OUTCOME:

- CURE----------resolution of all signs & symptoms of disease
- IMPROVEMENT-----significant amelioration of signs & symptoms of disease
- FAILURE---------persistence of signs & symptoms of disease

MYCOLOGICAL OUTCOME:

- ERADICATION-----negative KOH and negative fungal culture
- PERSISTENCE-----positive KOH and/or positive fungal culture

SECOND POST-TREATMENT VISIT:

Visit 3 (Day 37 of study - 30 days post-treatment - a window of 35-42 days was accepted:

To be considered evaluable for the second post-treatment visit, patients had to have met all inclusion and exclusion criteria, and had to return for the second post-treatment visit within the 28-35 day post-treatment window. The reviewing Medical Officer had to exclude more patients than the Applicant due to the larger window of return. A wider window was accepted to allow for weekends and holidays.

Within 28-35 days after completion of the 7 day treatment regimen, patients were re-evaluated for signs and symptoms. KOH prep and culture samples were repeated for evaluation of mycological cure. Patients were evaluated for clinical efficacy, for mycological efficacy and for therapeutic outcome.

CLINICAL OUTCOME:

CURE----------resolution of all signs and symptoms of disease
IMPROVEMENT-----significant amelioration of signs and symptoms of disease
FAILURE---------persistence of signs and symptoms of disease

COMMENT: The reviewer only accepted categories of CURE *(resolution of all signs and symptoms) or* FAILURE *(persistence of any sign or symptom of disease) at the second post-treatment visit.*

MYCOLOGICAL OUTCOME:

ERADICATION-----negative KOH and negative fungal culture
PERSISTENCE-----positive KOH and/or positive fungal culture

THERAPEUTIC OUTCOME:

CURE----------resolution of all signs and symptoms of disease at the second post-treatment visit (patients had to be considered either a cure or an improvement at the first post-treatment visit also) and have negative KOH and fungal culture results at all followup visits.
FAILURE---------persistence of signs and symptoms of disease or positive KOH and/or fungal culture

COMMENT: The reviewer considered only patients who had resolution of all signs and symptoms of disease at the second post-treatment visit (and patients had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture results at all visits to be THERAPEUTIC CURES.

Patients who were either a clinical failure and/or a mycological failure at either of the two follow-up visits were considered to be THERAPEUTIC FAILURES.

Any adverse reactions experienced by the patient, or noted by the investigating physician, were reported on an adverse event form. There were five events reported, all at visit 2. These will be described later in this report. The patients were also advised to record the severity of itching or burning daily from Day 1 until 30 days after completion of treatment. Concomitant medications could be used as required, provided neither the condition being treated nor the medication being taken affected the progression of the vaginal infection or therapeutic effects of the treatment.

Patients were fully informed regarding all aspects of the trial including potential side effects of the study medication.

RESULTS:

A total of fourteen investigators (9 gynecologists and 5 general practitioners) enrolled a total of 168 patients of whom 84 were randomized to the G&W 100mg vaginal insert and 84 were randomized to the Ortho Monistat-7 100mg insert. They were responsible to the [redacted] for the recruitment of patients to participate in the studies that were conducted for this ANDA. The curriculum vitae of each of the investigators was carefully reviewed and each was found to be qualified to conduct the study. The investigator, the geographical location of the investigator, and the number of patients enrolled for each investigator are listed in Table 1 below.

Table 1

Patient Enrollment By Investigator

Investigator/Location	Patients Given Miconazole (G&W)	Patients Given Monistat-7	Total
[redacted]	8	8	16
[redacted]	8	8	16
[redacted]	5	5	10
[redacted]	6	4	10
[redacted]	11	12	23
[redacted]	9	13	22
[redacted]	1	0	1
[redacted]	12	12	24
[redacted]	2	1	3
[redacted]	12	12	24
[redacted]	7	4	11
[redacted]	0	2	2
[redacted]	1	1	2
[redacted] .)	2	2	4
[redacted] TAL	84	84	168

A total of 168 patients was recruited for the study, as shown in Table 1, of which 117 were eligible for analysis and evaluable. Eligibility criteria included:

1. otherwise healthy females with at least one of the following clinical symptoms of vaginal candidiasis--itching, burning/irritation, vulvar erythema, edema or excoriations and/or vaginal erythema or edema;
2. positive KOH smear and culture for *Candida albicans* within one week of start of treatment;
3. age - ≥18, with no upper age limit;
4. patients must not be expected to begin menstruation during the treatment period; KOH and culture will be repeated if treatment start is delayed more than 7 days;
5. sexually active patients must be using a reliable method of birth control which does not interfere with the efficacy of the study medication;
6. patients must agree to abstain from douches, tub baths swimming, sexual intercourse and other activities likely to alter drug disposition in the vagina during treatment;
7. for the period following treatment, any sexual intercourse must involve the use of a condom.

There were 84 patients in the G&W arm of the study and 84 in the Ortho group. 24 G&W patients and 27 Ortho patients were excluded as ineligible for efficacy analysis (Table 2). 60 patients remained in the G&W group and 57 patients in the Ortho group.

Table 2

Exclusion From Efficacy Analysis
By Applicant G&W N = 51

Reason	G&W	Ortho
Negative culture on admission	12	11
Protocol violation (wrong laboratory, menses during treatment,etc.)	4	7
Lost to follow-up or missing data:		
Came for visit 1 only	1	3
Came for visit 1 & 2 only	2	0
Drop out for ADR	1	0
Came too early/late for visit 2 or 3	0	1
Missing KOH-culture at any visit	4	5
Total	**24**	**27**

Table 3

Ineligible For Efficacy Analysis N = 51

Investigator	Patient Number	G&W/Ortho	Reason
1. [illegible]	# 02	Ortho	3c
2. [illegible]	# 11	G&W	3c
3. "	# 12	G&W	2c
4. "	# 13	Ortho	3c
5. [illegible]	# 16	G&W	2a
6. [illegible]	# 17	G&W	3a
7. "	# 18	Ortho	2c
8. "	# 19	G&W	3c
9. "	# 20	Ortho	3c
10. [illegible]	# 25	Ortho	3a
11. [illegible]	# 38	Ortho	2c
12. [illegible]	# 44	Ortho	3a
13. [illegible]	# 50	Ortho	3a
14. "	# 54	G&W	3a
15. "	# 58	G&W	2c
16. "	# 60	G&W	3a
17. "	# 62	Ortho	2a
18. [illegible]	# 65	G&W	3a
19 "	# 67	G&W	3c
20. "	# 69	Ortho	3c
21. "	# 71	G&W	3c
22. "	# 72	Ortho	3a
23. "	# 74	G&W	3c
24. "	# 77	Ortho	3c
25. "	# 78	G&W	2c
26. "	# 80	G&W	3c
27. [illegible]	# 94	G&W	3c
28. [illegible]	# 96	Ortho	2a
29. [illegible]	# 98	Ortho	3c
30. "	# 100	G&W	3c
31. "	# 101	Ortho	3c
32. "	# 104	G&W	3c
33. "	# 109	Ortho	2c
34. [illegible]	# 113	G&W	3c

Table 3 - Continued

Investigator	Patient Number	G&W/Ortho	Reason
35. ~	# 115	Ortho	3a
36. "	# 120	Ortho	2a
37. "	# 121	Ortho	3a
38. "	# 122	Ortho	3a
39. "	# 123	G&W	5
40. ~	# 129	G&W	2b
41. "	# 130	Ortho	2c
42. "	# 131	Ortho	3c
43. "	# 132	G&W	3c
44. "	# 133	Ortho	3c
45. "	# 134	Ortho	3c
46. "	# 135	G&W	2b
47. "	# 136	G&W	3c
48. "	# 137	G&W	2c
49. "	# 138	Ortho	2c
50. ~	# 159	Ortho	2d
51. ~	# 166	Ortho	3c

CODE:

2a -	Patient came for visit 1 only	(4 patients)
2b -	Patient came for visit 1 & 2 only	(2 patients)
2c -	Missing KOH/culture at any visit	(9 patients)
2d -	Came too early/late for visit 2 or 3	(1 patient)
3a -	Protocol violation (Wrong laboratory, menses during treatment, etc.)	(11 patients)
3c -	Negative culture on admission	(23 patients)
5 -	Drop out for adverse drug reaction	(1 patient)

Table 4

Exclusion fom Efficacy Analysis
Per Investigator

Investigator (# enrolled in parenthesis)	Patients Given Miconazole (G&W)	Patients Given Monistat-7 (Ortho)	Total
(16)	2	3	5
(16)	6	3	9
(10)	5	5	10
(10)	0	1	1
(23)	1	5	6
(22)	1	1	2
(1)	1	0	1
(24)	0	1	1
(3)	2	1	3
(24)	3	3	6
(11)	1	0	1
(2)	0	1	1
(2)	0	1	1
(4)	2	2	4
Total (168)	24	27	51

Investigators: Fourteen investigators (9 gynecologists and 5 general practitoners) from various locations in Canada recruited patients who were evaluable for efficacy analysis. The patients of four investigators were ineligible for efficacy analysis-- representing eighteen out of the fifty one excluded by the Applicant for efficacy analysis. The investigators, their geographical location, and the number of evaluable patients for each are listed in Table 5 below:

Table 5
Patients Evaluable by Applicant G&W
For 1st and 2nd Re-visits

Investigator/Location	Patients Given Miconazole (G&W)	Patients Given Monistat-7	Total
[redacted]	6	5	11
[redacted]	2	5	7
[redacted]	0	0	0
[redacted]	6	3	9
[redacted]	10	7	17
[redacted]	8	12	20
[redacted]	0	0	0
[redacted]	12	11	23
[redacted]	0	0	0
[redacted]	9	9	18
[redacted]	6	4	10
[redacted]	0	1	1
[redacted]	1	0	1
[redacted]	0	0	0
TOTAL	60	57	117

The total number of patients evaluable by the Applicant was 117- 60 patients in the G&W group and 57 patients in the Ortho group. The Reviewing Medical Officer determined that there were 96 patients evaluable - 51 patients in the G&W group and 45 in the Ortho group after excluding an additional 21 patients for returning outside the accepted windows for visit 2 or visit 3. See Table 5a below:

Table 5a
Exclusion From Efficacy Analysis
By Medical Officer

Investigator	Applicant Evaluable	G&W	Ortho	Total
	23	0	0	0
	20	0	1	1
	18	2	3	5
	17	1	2	3
	11	3	5	8
	10	3	0	3
	9	0	0	0
	7	0	1	1
	1	0	0	0
	1	0	0	0
	0	0	0	0
	0	0	0	0
	0	0	0	0
Total	117	9	12	21

Table 5b
Patients Evaluable By Medical Officer

Investigator	G&W	Ortho	Total
	12	11	23
	8	11	19
	7	6	13
	9	5	14
	3	0	3
	3	4	7
	6	3	9
	2	4	6
	0	1	1
	1	0	1
	0	0	0
	0	0	0
	0	0	0
Total	51	45	96

Table 6

Demographic DATA

	Observed	Minimum-Maximum	Mean
G & W	N = 60	Ht (cm) 128-173 (51-68")	162 (63")
		Wt (kg) 46-93 (99-204#)	60 (132#)
		Age (yr) 16-52 (16-52yr)	31 (31yr)
Ortho	N = 57	Ht (cm) 150-177 (59-66")	162 (63")
		Wt (kg) 39-121 (86-266#)	63 (138#)
		Age (yr) 18-64 (18-64yr)	32 (32yr)

There was no statistically significant difference between the two groups in age, height, and weight.

The patients were not classified by race.

CLINICAL OUTCOME - PER APPLICANT

Table 7

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	54/60 (90%)	47/57 (82%)
Ortho	54/57 (94%)	44/55 (80%)

Table 7a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	55/60 (91%)	52/57 (91%)
Ortho	52/57 (91%)	52/55 (95%)

Table 7b

Therapeutic Cure Rate

Treatment Group	Visit 3
G&W	40/60 (67%)
Ortho	39/55 (71%)

Mycological cure was defined as KOH and culture results negative at both return visits 2 and 3. Clinical cure was defined as an improvement in symptoms at visit 2 as compared to visit 1 and absence of symptoms at visit 3. Therapeutic cure was defined as resolution of all signs and symptoms at visit 3 and negative KOH and fungal culture results at visit 2 and visit 3.

Note: The denominator values in Tables 7 & 7a at visit 3 differ from visit 2. Five (5) patients were not evaluated for mycological or clinical response because they did not return for visit 3. They were patients # 117,161,& 169 (G&W) and patients # 76 and 116 (Ortho).

CLINICAL OUTCOME - PER MEDICAL OFFICER

Table 8

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	45/51 (88%)	39/51 (76%)
Ortho	42/45 (93%)	38/45 (84%)

Table 8a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
G&W	43/51 (84%)	43/51 (84%)
Ortho	44/45 (98%)	41/45 (90%)

Table 8b

Therapeutic Cure Rate

Treatment Group	Visit 3
G&W	35/51 (69%)
Ortho	37/45 (82%)

Mycological cure was defined as KOH and culture results negative at both return visits 2 and 3. Clinical cure was defined as an improvement in symptoms at visit 2 as compared to visit 1 and absence of symptoms at visit 3. Therapeutic cure was defined as resolution of all signs and symptoms at visit 3 and negative KOH and fungal culture results at visit 2 and visit 3.

Clinical Outcome Summary:

At visit 2, the Applicant demonstrated a 90% mycological cure rate for the G&W product and a 94% mycological cure rate for the Ortho product. The Medical Officer found comparable results of 88% (G&W) and 93% (Ortho). At visit 3, the Applicant showed an 82% mycological cure rate for the G&W product and an 80%- mycological cure rate for the Ortho product. The Medical Officer's review found results of 76% (G&W) and 84% (Ortho) mycological cure rates. It remains for statistical analysis to determine if the differences are significant.

The clinical cure rate at visit 2 per the Applicant was 91% for both the G&W and the Ortho products. The Medical Officer's review determined clinical cure rates at visit 2 of 84% (G&W) and 98%(Ortho). At visit 3, the Applicant found a clinical cure rate of 91% for the G&W product and 95% for the Ortho product. The Medical Officer determined clinical cure rates at visit 3 of 84% (G&W) and 90% (Ortho).

The therapeutic cure rate for the G&W group of patients was 67% per the Applicant and 71% for the Ortho patients. The Medical Officer's review determined a 69% therapeutic cure rate for the G&W group and an 82% therapeutic cure rate for the Ortho group. Statistical analysis is necessary to determine if that difference is significant.

SAFETY ANALYSIS

A total of 17 patients reported 23 adverse events according to the Applicant. There were 17 in the G&W group and 6 in the Ortho group. One patient (#123 G&W) discontinued the study due to nausea, headache and vaginal burning. It was uncertain if this adverse event was due to the study medication. None of the remaining reported eents was unusual, considered serious, or definitely related to the study medication. See Table 9 ,page 21.

Table 9
Adverse Events

Treatment Group		Description	Visit	Related To Medication?
G&W	# 12	Upper respiratory infection	3	No
G&W	# 14	External irritation	2	Uncertain
G&W	# 21	Mild transient itching twice	2	No
		Irritation > colonoscopy	3	No
G&W	# 29	Mild transient nausea	2	No
		Mild intermittent burning		
G&W	# 43	Light abdominal pain for 7 days at beginning of treatment	2	Uncertain
G&W	# 45	Abdominal pain 10 minutes after application of vaginal suppository	2	Uncertain
G&W	#123	Nausea, headache, vaginal burning-pt. had to stop on 5th day of treatment	2	Uncertain
G&W	#141	External irritation	2	No
G&W	#147	Allergic reaction,facial pruritus; history of prior allergic reactions to many factors	2	No
G&W	#165	Pruritus 3 times daily for three days	2	Uncertain
			3	Uncertain
G&W	#167	Pruritus	2	No
Ortho	# 10	Burning after intercourse	2	Uncertain
Ortho	# 15	Spotting; not menses	2	Uncertain
Ortho	# 28	Pelvic pain	3	No
Ortho	# 32	Persistent irritation after treatment; ? allergy to capsule covering	2	Uncertain
			3	Uncertain
Ortho	#144	Intermittent vulvar itching	2	No
		Intermittent vulvar itching	3	No
Ortho	#164	Pruritus for 1 hour	2	No
		Pruritus and burning	3	No

SUMMARY:

The applicant, G&W Laboratories, Inc. , has submitted data from a multicenter study conducted by _____ which compares two formulations of Miconazole Nitrate Vaginal Suppository, 100 mg manufactured by the applicant G&W Laboratories and Monistat-7 by Ortho Pharmaceutical in treating patients with vulvovaginal candidiasis. Based on these data, the applicant is requesting approval of its miconazole 100 mg suppository for the seven day treatment of vulvovaginal candidiasis.

The criterion for demonstrating therapeutic equivalency for generic drugs is that the lower and upper limit of the 90% confidence interval on the difference between the two active products must be totally within the interval (-.20, +.20).

The data that has been submitted by the G&W Laboratories, Inc. have been verified and analyzed by me with statistical consultation from Ralph Harkins, PhD. of the Division of Biometrics. The applicant's visit 2 data comparing G&W's product to Ortho's Monistat-7 Vaginal insert for Mycological Cure Rates show the two products to be statistically equivalent. The reviewing medical officer (RMO)'s data concurs in this assessment. The applicant's visit 2 data comparing G&W's product to Ortho's Monistat-7 Vaginal insert for Clinical Cure Rates show the two products to be statistically equivalent. The RMO's data show the G&W product to be statistically inferior to the Ortho product as to Clinical Cure Rates.

The applicant's visit 3 data for Mycologic Cure Rates support the claim of equivalence of the two products. The RMO's data fail to support the claim of equivalency for Mycologic Cure Rates at visit 3, showing the G&W product to be slightly inferior to the Ortho product at this point. The applicant's visit 3 data for Clinical Cure Rates and the RMO's visit 3 data show both products to be statistically equivalent to one another.

The applicant's visit 3 data for Therapeutic Cure Rates supports the equivalency claim for the two products. The confidence interval based on the reviewing medical officer's data fail to support the equivalency claim, indicating the G&W product is possibly inferior to the Ortho product.

CONCLUSION:

The results of the analyses of these data fail to support the applicant's claim that the G&W Miconazole Vaginal Insert 100 mg is therapeutically equivalent to the Ortho Monistat-7 Vaginal Insert in the treatment of recurring vulvovaginal candidiasis.

RECOMMENDATION:

From a clinical standpoint, I do not recommend approval of G&W's formulation of Miconazole Nitrate Suppository, 100 mg for the treatment of vulvovaginal candidiasis.

In the study conducted by G&W, it has not been shown that their product is comparable to the Ortho product in efficacy.

/S/

Julius S. Piver, M.D.
Medical Officer (Ob-Gyn)

Concurrence Only:
HFD/520/Dir/MFanning /S/ 12/18/95
HFD/520/SMO/RAlbrecht
/S/ 12/12/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

STATISTICAL REVIEW(S)

Attachment - 2

Statistical Review and Evaluation
(Consult)

ANDA#: 74-414

OCT 4 1996

Applicant: G and W Laboratories, Inc..

Name of Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Documents Reviewed: Medical Officer's Review (5/23/96) submitted for Consult

Indication: Vaginal Candidiasis

Medical Input: Dr. Julius Piver, HFD-520

A. INTRODUCTION

This is a Generic Drug Product. Therefore, we use the 90% confidence interval (CI) for determining therapeutic and related equivalency statements. This is the same as using two one-sided 95% confidence intervals. The allowable confidence interval length in Generic Drug trials is 20% for cure/failure type trials and within 20% of the active control mean response for other type response variables. Since the concept is that the new agent is not to be either better than or worse than the control agent, the 90% CI must be completely contained within the -20% and +20% delta values.

Generic Drug Division trials of vaginal care products are generally standardized, therefore, a full statistical evaluation of the total submission is only done if problems in conduct or reporting of trial results are noted by the Reviewing Medical Officer (RMO). When there are no problems, our review is confined to check statistical results developed by the RMO or to compute confidence intervals on data as derived by the RMO. Since clinical trial data is not provided to the statistician, no evaluation of consistency among (between) investigators by treatment can be made. If the odds ratios differ significantly among the investigators, the following evaluation will not account for this.

B. CALCULATIONS AND EVALUATION

All calculations are based on data as supplied by the RMO. No effort has been made to check for internal consistency or to make other data validity checks. All confidence interval results are presented as two-sided 90% confidence intervals in the format $_{nt,\,nc}(CI)_{\,pt,\,pc}$, where n_t and p_t are respectively the sample size and success rates for the test agent (G&W's product - miconazole insert 100 mg) and n_c and p_c are similarly defined for the control agent (Ortho's product - Monistat-7 miconazole insert 100 mg).

Mycological and clinical response rates are secondary efficacy criteria and the therapeutic

response rate is the primary efficacy criterion.

The following CIs are based on the Sponsor's data. For clinical response at the first post-treatment visit (V2), comparing G&W (the sponsor's product) to Ortho yield the following 90% CI: $_{55,54}$ (-.163, .096)$_{.84,.87}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{49,51}$ (-.114, .069)$_{.94,.96}$. For mycological response at the first post-treatment visit (V2), the G&W versus Ortho 90% CI is $_{55,54}$ (-.157, .051)$_{.89,.94}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{49,51}$ (-.107, .174)$_{.86,.82}$.

For therapeutic response at second post-treatment visit (V3), the G&W versus Ortho 90% CI is $_{55,54}$ (-.156 .167)$_{.71,.70}$.

The following CIs are based on the Medical officer's data. For clinical response at the first post-treatment visit (V2), comparing G&W (the sponsor's product) to Ortho yield the following 90% CI: $_{55,53}$ (-.229, -.024)$_{.85,.98}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{55,53}$ (-.069, -.186)$_{.85,.92}$. For mycological response at the first post-treatment visit (V2), the G&W versus Ortho 90% CI is $_{55,53}$ (-.157, .053)$_{.89,.94}$. At second post-treatment visit (V3) the G&W versus Ortho 90% CI is $_{55,53}$ (-.178, .121)$_{.76,.79}$.

For therapeutic response at second post-treatment visit (V3), the G&W versus Ortho 90% CI is $_{55,53}$ (-.241 .075)$_{.69,.77}$.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The results of the analyses of data derived from the RMOs review fail to support the sponsor's claim that their formulation of Miconazole Nitrate Suppository, 100 mg is therapeutically equivalent to the active comparator agent.

/S/ 10/4/96

Daphne Lin, Ph.D.
Acting Team Leader, Biometrics IV

cc:
Orig. ANDA 74-414
HFD-520
HFD-520/Dr. Feigal
HFD-520/Dr. Leissa
HFD-520/Dr. Chi
HFD-630/Ms. Parise
HFD-725/Dr. Harkins
HFD-725/Dr. Lin
Chron.
This review contains 2 pages.

Attachment - 4

Statistical Review and Evaluation
(CONSULT)

ANDA#: 74-414

NOV 30 [illegible]

Applicant: G and W Laboratories, Inc.

Name of Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Drug Category: Anti Fungal

Documents Reviewed: Medical Officer's Review Submitted for Consult 11/27/95

Indication: Recurrent Vaginal Candidiasis.

Type Review: Clinical

Medical Input: Dr. Julius Piver, HFD-520

A. INTRODUCTION

This is a Generic Drug Product, therefore we use the 90% confidence interval (CI) for determining therapeutic and related equivalency statements. This is the same as using two-one sided 95% confidence intervals. The allowable delta in Generic Drug trials is 20% for cure/failure type trials and within 20% of the active control mean response for other type response variables. Since the concept is that the new agent is not to be either better than nor worse than the control agent, the 90% CI must be completely contained within the -20% and +20% delta values.

Generic Drug Division trials of vaginal care products are generally standardized. Therefore, a full statistical evaluation of the total submission is only done if problems in conduct or reporting of trial results are noted by the Reviewing Medical Officer (RMO). When there are no problems our review is confined to checking statistical results developed by the RMO or to computing confidence intervals on data as derived by the RMO. Since data is not provided by the investigator, no evaluation of consistency among (between) investigators by treatment can be made. If the odds ratios differ significantly among the investigators, the following evaluation will not detect this.

B. Calculations and Evaluation

All calculations are based on data as supplied by the RMO. No effort has been made to check for internal consistency or to make other data validity checks. All confidence interval results are presented as two-sided 90% confidence intervals in the format
${}_{nt,\,nc}(CI)_{pt,\,pc}$, where n_t and p_t are respectively the sample size and success rates for the test

agent and n_c and p_c are similarly defined for the control agent.

The sponsor's visit 2 Mycological data, comparing G&W (the sponsor's product) to Ortho yield the following 90% CI for Mycological cure rates: $_{60.57}(-.14..06)_{.90..94}$ whereas the same CI using the RMOs data is $_{51.45}(-.17..07)_{.88..93}$. These CIs indicate the two products are therapeutically equivalent at this time point.

The sponsor's visit 3 data, comparing G&W (the sponsor's product) to Ortho yield the following 90% CI for Mycological cure rates: $_{57.55}(-.11..16)_{.82..80}$ whereas the same CI using the RMOs data is $_{51.45}(-.23..07)_{.76..84}$. The sponsor's data show the GW product to be statistically equivalent to the Ortho product whereas the RMOs data shows the GW product to be slightly inferior to the Ortho product at this time point.

The sponsor's visit 2 data, comparing GW (the sponsor's product) to Ortho yield the following 90% CI for Clinical cure rates: $_{60.57}(-.10..10)_{.91..91}$ whereas the same CI using the RMOs data is $_{51.45}(-.24..-.02)_{.84..98}$. The sponsor's data show the GW product to be statistically equivalent to the Ortho product whereas the RMOs data show the GW product to be statistically inferior to the Ortho product at this time point.

The sponsor's visit 3 data, comparing G&W (the sponsor's product) to Ortho yield the following 90% CI for Clinical cure rates: $_{57.55}(-.13..07)_{.91..95}$ whereas the same CI using the RMOs data is $_{51.45}(-.19..06)_{.84..90}$. Both show the GW product to be statistically equivalent to the Ortho product.

The sponsor's visit 3 therapeutic data, which is the primary efficacy endpoint, comparing G&W (the sponsor's product) to Ortho yield the following 90% CI for the primary efficacy variable cure rates: $_{60.55}(-.19..12)_{.67..71}$ whereas the same CI using the RMOs data is $_{51.45}(-.30..03)_{.69..82}$. The sponsor's data show the two products to be statistically equivalent whereas the RMO's data indicate the GW product is possibly inferior to the Ortho product.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The results of the analyses of data derived from the RMOs review fail to support the sponsor's claim that their formulation of Miconazole Nitrate Suppository, 100 mg is therapeutically equivalent to the active comparator agent.

/S/

11/30/95

Ralph Harkins, Ph.D.
Biomedical Statistician
Acting Division Director
Biometrics Division

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

ADMINISTRATIVE DOCUMENTS

CDER Establishment Evaluation Report
for April 30, 1997

Application: **ANDA 74414/000**
Stamp: **12-OCT-1993** Regulatory Due:
Applicant: **GW LABS**
111 COOLIDGE ST
SOUTH PLAINFIELD, NJ 07080

Priority:
Org Code: **600**
Action Goal:
District Goal: **12-DEC-1994**
Brand Name:
Established Name: **MICONAZOLE NITRATE**
Generic Name:
Dosage Form: **SUP (SUPPOSITORY)**
Strength: **100 MG (VAGINAL)**

FDA Contacts: **N. NASHED (HFD-629) 301-594-1841 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 11-MAR-1997 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 01-AUG-1994 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
[redacted]

DMF No: [redacted]

[redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 04-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
[redacted]

Establishment: **2210277**
G AND W LABORATORIES INC
111 COOLIDGE ST
SOUTH PLAINFIELD, NJ 07080

DMF No:

Profile: **SUP** OAI Status: **POTENTIAL OAI**
Last Milestone: **OC RECOMMENDATI 11-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

See attached facsimile from Regina Braun, preapproval monitor in the New Jersey district. The "OAI alert" does not apply to this application.

/S/
4/30/97

Bob - My server is broken!

For 74-414 ~~de~~ New Jersey

has reccommended acceptable (3/10/97)

The OAI that applies to suppositories would not ~~apply~~ to this particular ~~Micanazole~~ miconazole nitrate product. A ~~n~~ Vaginal Cream was ~~Nitrate~~ covered during ~~that~~ that inspection ~~that~~ received an approve recommendation fa a micro testing change.

n ISI - 4/29/97

E L E C T R O N I C M A I L M E S S A G E

Date: 30-Apr-1997 08:12am EDT
From: Robert West
WESTR
Dept: HFD-611 MPN2 273
Tel No: 301-594-1837 FAX 301-594-0183

TO: See Below

Subject: ANDA 74-414 for G&W's Miconazole Nitrate Vaginal Suppositorie

Shirnette:

Re: ANDA 74-414 for G&W's Miconazole Nitrate Vaginal Suppositories

As we have previously discussed, there is an OAI Alert in EES for the G&W facility at 111 Coolidge Street, South Plainfield, NJ.

I have spoken to the preapproval monitor in New Jersey district, Regina Brown, and she has informed me that this OAI Alert does NOT pertain to ANDA 74-414 for G&W's Miconazole Nitrate Vaginal Suppositories. She said it pertained to ɔmethacin Suppositories. I have a fax from her to that effect.

I request that you confirm my understanding and delete the "OAI Alert" in theEES for this facility. Once this is done, we are prepared to approve this application.

Thanks,

Bob

Distribution:

TO: Shirnette Ferguson (FERGUSONS)

CC: Mark Lynch (LYNCHM)
CC: Jason Gross (GROSSJ)
CC: Joseph Buccine (BUCCINE)
CC: Nashed Emil Nashed (NASHEDN)
CC: Paul Schwartz (SCHWARTZP)

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 30-Apr-1997 08:59am EDT
From: Melissa Egas
EGASM
Dept: HFD-324 MPN1 265
Tel No: 301-827-0062 FAX 301-827-0145

TO: Robert West (WESTR)

Subject: RE: FWD: ANDA 74-414 for G&W's Miconazole Nitrate Vaginal Supposi

I'll fix it once I can get into the systam. There's no way to place a firm on product specific OAI alert, which there should be. Unfortunately, we can only use profile classes, and you'll need to call us if there is a question.

Mimi

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 17, 1997

FROM: Mary Fanning, MD
Associate Director for Medical Policy
Office of Generic Drugs

/S/ 4/24/97

Jerry Phillips, RPh
Director, Division of Labeling and Program
Office of Generic Drugs

/S/ 4/28/97

SUBJECT: Acceptability of ——— in ANDA 74-414

TO: For-the-Record (ANDA 74-414)

Ouestions of acceptability of the quantitative amount of ——— (Hydrogenated Vegetable Oil) in this formulation have been raised throughout the application. The formulation of this product is:

Miconazole Nitrate USP (Micronized)..... 100 mg
Hydrogenated Vegetable Oil (———
Hydrogenated Vegetable Oil (———

When accepted for filing, a copy of a Drug Product Reference File (DPRF) listing for NDA 17-450 for Monistat-7 Vaginal Cream, indicated that the formulation had been approved and subsequently discontinued with ——— of Vegetable Oils, Hydrogenated.

The bioequivalence reviewer (Dr. Surendra Shrivastava) noted on February 3, 1997, "that both ——— are hydrogenated vegetable oils. While the ——— is within the IIG limits, ——— is not listed in the 1996 IIG. However, ——— has been used in approved application 73-507 (miconazole nitrate vaginal suppository) ——— . Since it is a hydrogenated vegetable oil, and in the clinical study no side effects were noted, product <u>should</u> be safe". In an E-mail date 2-5-97 to Mary Fanning (OGD) and Brad (NDE), Surendra addresses the safety issue. Brad Leissa responded back that there were no local (vaginal) safety concerns raised in the clinical study and that, from a clinical perspective, that no safety concern exists.

In the Office Level Bioequivalence Review and sign-off, these facts were noted and the conclusion was made that the product should be safe. Subsequently, an E-mail from the Project Manager (Joe Buccine) dated March 28, 1997 questioned the wording "should be safe" as seen in the Office Level Bioequivalence sign-off.

Upon Office Level Review by Jerry Phillips, it was noted that although the clinical study revealed no side effects with this formulation, there was a warning on the labeling of the RLD and this product that states "Hydrogenated vegetable oil may weaken latex in condoms or in diaphragms. These suppositories contain hydrogenated vegetable oil. Do not rely on condoms or diaphragms... while using miconazole nitrate vaginal suppositories". The effect of hydrogenated vegetable oil on the condom or diaphragm would NOT have likely been detected in the clinical study.

Upon review of the Drug Product Reference File, many products have been approved with Hydrogenated Vegetable Oil [redacted] and [redacted], although this is NOT reflected in the IIG. In addition to the discontinued formulation in NDA 17-450, we have discovered that NDA 19-641 for Terazol 3 Vaginal Suppository has the following inactive ingredient formulation:

[redacted] .....
[redacted] .....
Butylated Hydroxyanisol.....

Although the duration of treatment of Terazol is only 3 days, the effect on a condom or diaphragm would be the same. Based upon these approved formulations, the clinical study results performed by the applicant, and the clearly labeled warning, we find no regulatory or safety concerns with this ANDA.

APPEARS THIS WAY
ON ORIGINAL

X:\NEW\FIRMSAM\G&W\74414.FTR

Redacted 2

pages of trade secret and/or confidential commercial information

E L E C T R O N I C M A I L M E S S A G E

Date: 14-Apr-1997 03:24pm EDT
From: Robert West
WESTR
Dept: HFD-611 MPN2 273
Tel No: 301-594-1837 FAX 301-594-0183

TO: See Below

Subject: FWD: Re: G & W Miconazole Vaginal Suppositories

Here's some follow up from the district regarding G&W's ANDA 74-414 for Miconazole Vaginal Suppositories. Since the reinspection has been assigned, it shouldn't be long before it's done. Since we've waited this long, I suggest we wait a short while longer for the district to give us the green light to approve.

Bob

Distribution:

	Jerry Phillips	(PHILLIPSJ)
CC:	Joseph Buccine	(BUCCINE)
CC:	Nashed Emil Nashed	(NASHEDN)
CC:	Paul Schwartz	(SCHWARTZP)
CC:	Kassandra Sherrod	(SHERRODK)
CC:	Mark Anderson	(ANDERSONM)

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 14-Apr-1997 10:05am EDT
From: Jason Gross
GROSSJ
Dept: HFD-324 MPN1 265
Tel No: 301-827-0062 FAX 301-827-0145

TO: Robert West (WESTR)
TO: Joseph Buccine (BUCCINE)

CC: Mark Lynch (LYNCHM)

Subject: FWD: Re: G & W

RE: G&W

Bob:

Attached is an E-mail from our NJ-DO with respect to G&W...

The OAI is in effect and it appears that this application will also be affected until it is resolved....

Well. . . 1 out of 1 today is not bad.

JAG

E L E C T R O N I C M A I L M E S S A G E

Date: 14-Apr-1997 09:53am EDT
From: rbrown4
rbrown4@ora.fda.gov@INTERNET@D
Dept:
Tel No:

TO: GROSSJ (GROSSJ@A1)

Subject: Re: G & W

I talked to the CO for this one and the followup inspection assignment has been issued, but it has not been started yet...In retrospect, I probably should have made this one withold until the follow-up is done, since testing and suppositories had a big part in issuance of the warning letter...Let me know if a change in the EES DO recommendation is necessary for an adeuate response to the reviewer...I don't think they should get approved for anything until we have been back out there...Regina

E L E C T R O N I C M A I L M E S S A G E

Date: 14-Apr-1997 08:13am EDT
From: Jason Gross
GROSSJ
Dept: HFD-324 MPN1 265
Tel No: 301-827-0062 FAX 301-827-0145

TO: REGINA T BROWN (ORA) (RBROWN4@ORA.FDA.GOV @INTERNET)

CC: Robert West (WESTR)
CC: Joseph Buccine (BUCCINE)

Subject: G & W

G & W Labs
CFN 2210277
OAI alert issued sent to us 1-17-97
Profile classes, Sup, Oin, liq

Regina...

Good morning, hope you had a great weekend.....

With respect to this firm, The Office of Generic Drugs is ready to approve an application they have had pending for a long.. long time (N 74414/000, Miconazole Vag Supp). For this application their is an AC-milestone dated March 10-1997 that says "DO ACCEPTABLE RECOMMENDATION SENT 7/29/94."

Two questions...

1. Is the OAI alert still in effect or has the issues been resolved?

2. If the OAI alert is in effect, is this application (74-414) affected, or can we go with the approval recommendation from you dated 3-10-97

Thanks
JAG

APPROVAL SUMMARY FOR 74-414

ANDA: 74-414

FIRM: G & W Laboratories, Inc.

DRUG: Miconazole Nitrate

DOSAGE: Suppository

STRENGTH: 100 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 3/11/97

BIO STUDY/BIOEQUIVALENCE STATUS: The clinical study has been found acceptable 2/3/97

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C and 23 months controlled room temperature.

LABELING REVIEW STATUS: The labeling is satisfactory by L. Golson 2/7/97

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted a copy of the exhibit batch lot # 0197-PB-13-A for —

The firm has provided the master formula and manufacturing procedure for intended production batches suppositories per batch. The firm will be using the same drug substance DMF The DMF is satisfactory 5/17/94. The intended production batches will be manufactured using the same manufacturing procedure, and equipment as of the exhibit batch.

COMMENTS: The Application is Approvable.

/S/ 3/24/97

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 3/24/97

SUPERVISOR: Paul Schwartz, Ph.D.

/S/ 3/24/97

CDER Establishment Evaluation Report
for April 07, 1997

Application: **ANDA 74414/000**
Stamp: **12-OCT-1993** Regulatory Due:
Applicant: **GW LABS**
111 COOLIDGE ST
SOUTH PLAINFIELD, NJ 07080

Priority:
Org Code: **600**
Action Goal:
District Goal: **12-DEC-1994**
Brand Name:
Established Name: **MICONAZOLE NITRATE**
Generic Name:
Dosage Form: **SUP (SUPPOSITORY)**
Strength: **100 MG (VAGINAL)**

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 11-MAR-1997 by FERGUSONS
ACCEPTABLE on 01-AUG-1994 by DAMBROGIOJ

Establishment:

DMF No:

Responsibilities:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 04-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **2210277**
G AND W LABORATORIES INC
111 COOLIDGE ST
SOUTH PLAINFIELD, NJ 07080

DMF No:

Profile: **SUP** OAI Status: **POTENTIAL OAI**
Last Milestone: **OC RECOMMENDATI 11-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

Printed by Joseph Buccine

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Mar-1997 09:44am
From: Joseph Buccine
BUCCINE
Dept: HFD-617 MPN2 E209
Tel No: 301-827-1050 **FAX:** 301-827-1271

TO: Robert West (WESTR)

CC: Mark Anderson (ANDERSONM)
Subject: Miconazole Vag Supps 100 mg by G&W 74-414

Bob:

The ANDA is ready for approval. I'm putting together an AP pkg. In doing so, I noticed a possible problem that may need your attention.

As you may know, the inactive ingredients in this product differs from the Ortho's listed reference.

The issue of concern can be found in the office bio review. The review contains the following statement: Since it is a hydrogenated vegetable oil (referring to the difference in inactive ingredients), and in clinical study no side effects were noted, (the) product should be safe. I have concern with this sentence, especially the part that says "should be safe."

As a regulatory body, we approve drugs that ARE SAFE, not drugs that should be safe. Bio's statement implies that safety has not been fully determined.

I believe Bio knowingly worded the sentence this way because the safety of one of the inactive ingredients, [redacted] was not fully addressed. An e-mail dated 5Feb97 from Dr. Shrivastava to Dr. Fanning and Dr. Leissa specifically addresses the safety issue. Dr. Leissa response supports safety but is not definite. "From a clinical perspective, I don't think this poses a safety concern."

Perhaps I'm nit picking with semantics, but I'd prefer our clinician, Dr. Fanning, to say THIS DRUG IS SAFE BASED ON.... Alternatively, Bio should delete or revise their sentence so that they are not inferring that this product is less than proven safe.

The routing of the approval package will begin today. I hope this issue is resolved by the time the package gets to you.

Thanks, Joe

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report
for March 12, 1997

Application: **ANDA74414** Priority: Org Code: **600**
Stamp: **12-OCT-1993** Regulatory Due: Action Goal: District Goal: **12-DEC-1994**
Applicant: **GW LABS**
111 COOLIDGE ST
SOUTH PLAINFIELD, NJ 07080
Brand Name:
Established Name: **MICONAZOLE NITRATE**
Generic Name:
[redacted] **(SUPPOSITORY)**
[redacted]

FDA Contacts: **N. NASHED** **(HFD-625)** [redacted] Review [redacted]

Establishment: [redacted] Responsibilities: [redacted]

DMF No: [redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 04-MAR-1997**
Last Comp. St.: **ACCEPTABLE 04-MAR-1997**

Establishment: **2210277** Responsibilities:
G AND W LABORATORIES INC **FINISHED DOSAGE MANUFACTURER**
111 COOLIDGE ST
SOUTH PLAINFIELD, NJ 07080 DMF No:

Profile: **SUP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 11-MAR-1997**
Last Comp. St.: **ACCEPTABLE** **11-MAR-19[redacted]**
Profile: **TCM** OAI Status: **NONE**
Last Milestone: **REQUEST CANCELLE 12-FEB-1997**
Last Comp. St.: **NONE**

Overall Recommendation:

ACCEPTABLE	**on 11-MAR-1997**	**by S. FERGUSON**	**(HFD-324)**	**301-827-0062**
ACCEPTABLE	**on 01-AUG-1994**	**by J. D AMBROGIO**	**(HFD-324)**	**301-827-0062**

APPEARS THIS WAY
ON ORIGINAL

[redacted]

RECORD OF TELEPHONE CONVERSATION

Reference is made to our bio letter dated 2/6/97. In that letter, the sponsor was requested to develop comparative dissolution methods and specifications, and submit the data to the Agency for review asap.

~~Immediately~~ Prior to this telecon, Mr. Buccine clarified with Dr. Pathaik and Dr. Park that an acceptable response to this request is not a precondition for approval. However, the sponsor must commit to responding to this request post approval. No response was received to date.

The purpose of this telecon was to get ~~Perrigo~~ the firm to agree to submit a commitment to develop dissolution methods and specifications, and submit the data to the Agency within a reasonable time frame post approval.

Ms. ~~Green~~ Frankel agreed to forward our request. ~~Perrigo's commitment will be sent by FAX and followed by a hard copy to the file.~~

cc:
NDA
Division File
T-con Binder

Ms. Frankel would like to submit this commitment + revised specs (see 3/4/97 T-con) together this week.

DATE
3/~~7~~/97

ANDA NUMBER
74-~~395~~ 414

IND NUMBER

TELECON

INITIATED BY FDA

PRODUCT NAME
Miconazole Nitrate Vaginal Suppositories, 100 mg

FIRM NAME
G & W

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Frankel
~~Virginia Green~~

TELEPHONE NUMBER
~~616-673-7604~~

SIGNATURE
Joseph Buccine
/S/
3/~~7~~/97

The network is down. Therefore, this T-con is hand edited from a similar request.

/S/ 3-7-97

RECORD OF TELEPHONE CONVERSATION

FDA initiated the phone call to propose the following specifications.

DRUG SUBSTANCE:

The DSS identifies residual solvents [redacted] and sets limits. G&W should establish specs for these solvents that are consistent with that of the DSS.

FINISHED PRODUCT:

G&W should establish a spec of not more than [redacted] of related compounds regarding individual impurities.

G&W should establish a spec of not more than [redacted] of related compounds regarding stability testing.

Ms. Frankel said she understood the request and would forward our recommendations to G&W. A follow up telecon will be scheduled if needed.

cc:
ANDA 74-414
Division File
Telecon File Binder

x:\new\firmsam\G&W\telecons\744
14.002

3/11/97 Ms. Frankel said that the revised specs will be available by 3/21/97. /S/ 3/11/97

DATE
3/4/97

ANDA NUMBER
74-414

IND NUMBER

TELECON

INITIATED BY FDA
Paul Schwartz
Nashed Nashed
Joseph Buccine

PRODUCT NAME
Miconazole
Nitrate Vag Supps
100 mg

FIRM NAME
G&W

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Frankel

TELEPHONE NUMBER

SIGNATURE
Joseph Buccine
/S/ 3/4/97

FILE COPY

Printed by Lizzie Sanchez

Electronic Mail Message

Date: 05-Feb-1997 05:52pm
From: Surendra Shrivastava
SHRIVASTAVAS
Dept: HFD-655 MPN2 130
Tel No: 301-594-0350 FAX 301-594-0181

TO: Mary Fanning (FANNINGM)
TO: Brad Leissa (LEISSAB)

CC: Rabindra Patnaik (PATNAIK)
CC: Shriniwas Nerurkar (NERURKAR)
CC: Lizzie Sanchez (SANCHEZL)
Subject: ANDA 74-414 Miconazole Nitrate Suppository

Dr. Leissa and Dr. Fanning:

The medical and statistical reviews on this product has been finished, and the application is acceptable.

However, we have a question and concern about safety of one of the inactive ingredients used in the product - [redacted] which is present in large quantity, [redacted]/suppository. Apparently, this is hydrogenated vegetable oil and there should be little problem, if any. However, it is not listed under vaginal suppository in the Inactive Ingredient Guide (IIG 1996). On discussion with some chemists here at OGD, we found out that [redacted] has been used in an approved ANDA 73-507, [redacted]/suppository.

The question is, should we go ahead and approve the application? Do we have any other application where [redacted] was used in larger quantity? Please advise me with the appropriate route of action.

Thank you for an early response.

Surendra

APPEARS THIS WAY
ON ORIGINAL

Printed by Lizzie Sanchez

Electronic Mail Message

FILE COPY

tivity: COMPANY CONFIDENTIAL

Date: 05-Feb-1997 06:08pm
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2186 FAX 301-827-2325

TO: See Below
Subject: Re: ANDA 74-414 Miconazole Nitrate Suppository

Is ANDA 73-507 an approved vaginal candidiasis generic drug? What was the basis for accepting [redacted] in ANDA 73-507, [redacted] mg/suppository vs. [redacted] /suppository)? Assuming ANDA 73-507 is a vaginal suppository, did this one slip through the " Inactive Ingredient Guide (IIG 1996)" net?

As far as I recall, there were no local (vaginal) safety concerns raised in the vaginal candidiasis study.

From a clinical perspective, I don't think this poses a safety concern. However, I concede that there may other OGD regulatory issues which I can't address.

BL

> Dr. Leissa and Dr. Fanning:
>
> The medical and statistical reviews on this product has been finished, and the application is acceptable.
>
> However, we have a question and concern about safety of one of the inactive ingredients used in the product - [redacted] which is present in large quantity, [redacted] suppository. Apparently, this is hydrogenated vegetable oil and there should be little problem, if any. However, it is not listed under vaginal suppository in the Inactive Ingredient Guide (IIG 1996). On discussion with some chemists here at OGD, we found out that [redacted] has been used in an approved ANDA 73-507, [redacted] /suppository.
>
> The question is, should we go ahead and approve the application? Do we have any other application where [redacted] was used in larger quantity? Please advise me with the appropriate route of action.
>
> Thank you for an early response.
>
> Surendra
>

Distribution:

Attachment - 9

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 19-Dec-1996 02:30pm EST
From: David Feigal
FEIGALD
Dept: HFD-530 CRP2 N413
Tel No: 301-827-2330 FAX 301-827-251

TO: 2 addressees

CC: 6 addressees

Subject: Re: G & W application (ANDA 74-414)

I concur with the rcommendation to make the final decision an APPROVAL.

David Feigal

APPEARS THIS WAY
ON ORIGINAL

Attachment-8

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 19-Dec-1996 12:54pm EST
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-232[illegible]

TO: David Feigal (FEIGALD)

CC: 6 addressees

Subject: G & W application (ANDA 74-414)

David,

In a recent e-mail exchange with Mary Fanning, we discussed her reanalysis (in light of the applicant's resubmission) of an ANDA that was previously acted on. In Julius Piver's orginal review of this application, a not approvable was recommended. Like many of these, in light of Piver's review, the 90% CI just barely missed the "standard" lower limit of -20% difference on the lower end.

ve taken the liberty to extract the pertinent portions of our discussion.

IN HER ORIGINAL MESSAGE TO ME SHE STATED:

>#15,32,79 are all the same.
>
> V1 V2 V3
>symptoms 1 1 0
>mycology K+/C+ K-/C- K-/C-
>
>V1 to V2 is no change is this a failure or cure because the symptoms
>disappeared at V3?
> Applicant says F; FDA says C

I RESPONDED TO MARY:

>For pts. #15, 32, 79, [redacted] would say "fail" due to no
>change from V1 to V2 (even though the patients' S&S appear to have
>spontaneously resolved by V3). I agree with changing them to failures.

MARY RESPONDED TO ME:

>Since 520 did the original review and recommendation, I will need your
>concurrence for changing the decision regarding approval status of this
>product. With the agreed on attribution of patients which partly differ
>from the applicant's and also differ somewhat from Dr. Piver's review,
>the following cure rates and 90% CI are as follows:

>
>
>
>Therapeutic cure rate:

	G & W	Ortho
	38/55 (69%)	38/53 (71.7%)

>
>The difference between test and RLD is - 2.61, and the 90% CI with the
>correction factor is -18.91, 13.69.
>
>This will make the drug approvable and if all other issues have been
>worked out, in the end it will be an approval.
>
>We need to have your +/- Dr. Feigal's (if necessary) concurrence in
>writing and an e-mail will do.
>
>Mary

In sum, I agree that DAIDP's recommendation should be changed from NOT APPROVABLE to APPROVAL.

If you concur, please forward your e-mail concurrence for this recommendation to OGD.

.lanks,

Brad

APPEARS THIS WAY
ON ORIGINAL

Attachment - 5

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 12-Dec-1996 09:30am EST
From: Mary Fanning
FANNINGM
Dept: HFD-006 WOC2 6027
Tel No: 301-594-6740

TO: Brad Leissa (LEISSAB)

CC: Mark Anderson (ANDERSONM)

Subject: G&W application #74-414

Brad,

The company asked for identification of the patients that led to different numbers of evaluable patients and therapeutic cure. I have taken out my sleuth outfit (you didn't know I was a sleuth did you?) and ambled through the knotty forest of someone else's work. At last, Success!

According to the review here is the discrepancy:

Applicant: test (G&W) 39/55(71%) Ortho 38/54(70%)
It passes 90% CI.

FDA: test 38/55(69%) Ortho 41/53(77%0
It fails 90% CI.

Obviously the company wants to be sure this is right as it has led to a non-approval. I found the divergent patients and will describe them. Based on my conclusions about these patients (I have reviewed the primary case record forms) the application would be approvable.

G&W #124 Applicant says Improved; FDA says Failure based on the following:

	V1	V2	V3
symptoms -	score 2*	score 1*	score 1
mycology -	K+/C+	K-/C-	K-/C-

score 2= moderate itching, some swelling and erythema
score 1= mild itching and burning

I would call this a Failure, based on lack of resolution of clinical symptoms at V3, despite improvemant at V2.

:tho #75 Applicant says evaluable; FDA says non-evaluable
V3 visit window not met; pt. seen at Day 29 (window is day 34-43)

I would call this patient

#15,32,79 are all the same.

	V1	V2	V3
symptoms	1	1	0
mycology	K+/C+	K-/C-	K-/C-

V1 to V2 is no change is this a failure or cure because the symptoms disappeared at V3?

Applicant says F; FDA says C

If we take these three to be failures then the drug passes. If we take them to be cures the drug fails.

Please advise on the classification of these patients since the review occured under 520 and 520 signed off on it. In my patient evaluations for Foguera I am calling this type of response a no change and therefore a failure.

Thanks for your help.

Mary

I've sent you a fax but this is more succint and I might get your answer more quickly if via e-mail. Those papers to look at seem to disappear om my desk!

Attachment- 6

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 12-Dec-1996 09:53am EST
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-2325

TO: Mary Fanning (FANNINGM)

CC: Mark Anderson (ANDERSONM)
CC: Joseph Winfield (WINFIELD)

Subject: Re: G&W application #74-414

Mary,

APPEARS THIS WAY
ON ORIGINAL

Comments below:

>Brad,
>
>The company asked for identification of the patients that led to
>different numbers of evaluable patients and therapeutic cure. I have
taken out my sleuth outfit (you didn't know I was a sleuth did you?) and
ambled through the knotty forest of someone else's work. At last,
>Success!
>
>According to the review here is the discrepancy:
>
> Applicant: test (G&W) 39/55(71%) Ortho 38/54(70%)
> It passes 90% CI.
>
> FDA: test 38/55(69%) Ortho 41/53(77%0
> It fails 90% CI.
>
>Obviously the company wants to be sure this is right as it has led to a
>non-approval. I found the divergent patients and will describe them.
>Based on my conclusions about these patients (I have reviewed the
>primary case record forms) the application would be approvable.
>
>G&W #124 Applicant says Improved; FDA says Failure based on the
>following:

	V1	V2	V3
symptoms -	score 2*	score 1*	score 1
mycology -	K+/C+	K-/C-	K-/C-

>
>score 2= moderate itching, some swelling and erythema
score 1= mild itching and burning

>I would call this a Failure, based on lack of resolution of clinical
>symptoms at V3, despite improvemant at V2.
>
>Ortho #75 Applicant says evaluable; FDA says non-evaluable
> V3 visit window not met; pt. seen at Day 29 (window is

>day 34-43)
>
>I would call this patient ——
>
>#15,32,79 are all the same.
>

	V1	V2	V3
>symptoms	1	1	0
>mycology	K+/C+	K-/C-	K-/C-

>
>V1 to V2 is no change is this a failure or cure because the symptoms
>disappeared at V3?
> Applicant says F; FDA says C

Everything above...I agree with you.

In this last scenario for pts. #15, 32, 79, —— would say "fail" due to no change from V1 to V2 (even though the patients' S&S appear to have spontaneously resolved by V3). I agree with changing them to failures.

>If we take these three to be failures then the drug passes. If we take
>them to be cures the drug fails.

>Please advise on the classification of these patients since the review
>occured under 520 and 520 signed off on it. In my patient evaluations
>for Foguera I am calling this type of response a no change and therefore
>a failure.
>
>Thanks for your help.
>
>Mary
>
>I've sent you a fax but this is more succint and I might get your answer
>more quickly if via e-mail. Those papers to look at seem to disappear
>from my desk!

Based on your introductory statement, by changing patients #15, 32, and 79 to failures, I assume G&W now meets the 90% CI. Correct?

Brad

Attachment - 7

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 12-Dec-1996 11:43am EST
From: Mary Fanning
FANNINGM
Dept: HFD-006 WOC2 6027
Tel No: 301-594-6740

TO: Brad Leissa (LEISSAB)

CC: Mark Anderson (ANDERSONM)
CC: Gordon Johnston (JOHNSTONG)

Subject: G & W application

Brad,

I think I've lost my last e-mail on this topic and perhaps I've already addressed this.

Since 520 did the original review and recommendation, I will need your concurrence for changing the decision regarding approval status of this product. With the agreed on attribution of patients which partly differ from the applicant's and also differ somewhat from Dr. Piver's review, the following cure rates and 90% CI are as follows:

	G & W	Ortho
Therapeutic cure rate:	38/55 (69%)	38/53 (71.7%)

The difference between test and RLD is - 2.61, and the 90% CI with the correction factor is -18.91, 13.69.

This will make the drug approvable and if all other issues have been worked out, in the end it will be an approval.

We need to have your +/- Dr. Feigal's (if necessary) concurrence in writing and an e-mail will do.

Mary

Attachment - 3
1

M E M O R A N D U M

DATE: May 23, 1996

TO: Director, Office of Generic Drugs
HFD-615
7500 Standish Place
Rockville, Maryland 20855

FROM: Julius Piver, M.D.
Medical Officer, DAIDP, HFD-520

THROUGH: Brad Leissa, M.D. /S/ 10/4/96
SMO, DAIDP, HFD-520

David Feigal ~~Mary Fanning~~, M.D., MPH ~~Ph.D.~~
Director, DAIDP, HFD-520

SUBJECT: Consultation on ANDA 74-414

Please find attached to this memorandum, the medical consultation from HFD-520 which was requested. If there are any questions regarding this matter, please do not hesitate to contact the Division at 443-4110

Thank you for this consultation.

APPEARS THIS WAY
ON ORIGINAL

FILE

Division of Anti-Infective Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-520
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: 3.5.96 Number of Pages (including cover sheet) 8

TO: Jason Gross

COMPANY: Office of Generic Drugs - HFD 615 MPN2 113

FAX NUMBER: 301 594-0181

MESSAGE: Here is the information requested re: 74-414

Kindly acknowledge receipt.

Thank you.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Julius Piver, M.D.

TITLE: Medical Officer HFD-520

TELEPHONE: 301 827-2181 FAX NUMBER: 301-827-2327

2-1

Project No. 901287

Comparison of Miconazole 100 mg Suppositories (G&W) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

All eligible, enrolled patients: Treatment Group = G & W (69)

Subject	Baseline KOH	Baseline Cult	Baseline Symptoms	1st Re-Visit KOH	1st Re-Visit Cult	1st Re-Visit Symptoms	1st Re-Visit #Days	2nd Re-Visit KOH	2nd Re-Visit Cult	2nd Re-Visit Symptoms	Mycol cure	Clin cure	#Days
1 ✓	Positive	Positive	Mild	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	38
3 ✓	Positive	Positive	Mild	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	39
6 ✓	Positive	Positive	Mild	Negative	Negative	Mild	16	Negative	Negative	None	Yes	No	51
7 ✓	Positive	Positive	Mild	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	37
14 ✓	Positive	Positive	Mild	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	37
21 ✓	Positive	Positive	Moderate	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	44
22 ✓	Positive	Positive	Mild	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	36
26 ✓	Positive	Positive	Mild	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	37
27 ✓	Positive	Positive	Mild	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	35
29 ✓	Positive	Positive	Mild	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	37
30 ✓	Positive	Positive	Mild	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	37
33 ✓	Positive	Positive	Moderate	Negative	Negative	None	19	Negative	Negative	None	Yes	Yes	43
36 ✓	Positive	Positive	Moderate	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	44
39 ✓	Positive	Positive	Severe	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	44
40 ✓	Positive	Positive	Moderate	Negative	Negative	None	20	Negative	Negative	None	Yes	Yes	43
42 ✓	Positive	Positive	Mild	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	43
43 ✓	Positive	Positive	Severe	Negative	Negative	None	20	Negative	Negative	None	Yes	Yes	43
45 ✓	Positive	Positive	Moderate	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	42
48 ✓	Positive	Positive	Severe	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	43
49 ✓	Positive	Positive	Moderate	Positive	Positive	None	15	.	.	.	No	No	37
51 ✓	Positive	Positive	Moderate	Negative	Negative	Mild	14	Positive	Negative	Mild	No	No	39
55 ✓	Positive	Positive	Severe	Negative	Negative	Severe	21	Negative	Negative	Severe	Yes	No	43
61 ✓	Positive	Positive	Moderate	Negative	Negative	None	17	Negative	Negative	None	Yes	Yes	41
64 ✓	Positive	Positive	Severe	Negative	Negative	None	19	Negative	Negative	None	Yes	Yes	43
70 ✓	Positive	Positive	Mild	Negative	Negative	Moderate	15	Negative	Negative	None	Yes	No	39
73 ✓	Positive	Positive	Severe	Negative	Negative	Mild	15	Negative	Negative	None	Yes	Yes	43
82 ✓	Positive	Positive	Severe	Negative	Negative	None	17	Negative	Negative	None	Yes	Yes	39
84 ✓	Positive	Positive	Severe	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	40
87 ✓	Positive	Positive	Severe	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	36
88 ✓	Positive	Positive	Severe	Positive	Positive	Mild	14	.	.	.	No	Yes	36
90 ✓	Positive	Positive	Mild	Negative	Negative	Mild	20	Negative	Positive	None	No	No	47
92 ✓	Positive	Positive	Moderate	Negative	Negative	Mild	21	Negative	Negative	Mild	Yes	No	53
95 ✓	Positive	Positive	Moderate	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	42
97 ✓	Positive	Positive	Moderate	Negative	Negative	Mild	18	Negative	Negative	None	Yes	Yes	40
102 ✓	Positive	Positive	Moderate	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	40
106 ✓	Positive	Positive	Moderate	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	48
107 ✓	Positive	Positive	Moderate	Negative	Negative	None	18	Negative	Positive	None	No	Yes	43

(6)

3 of 1

Comparison of Miconazole 100 mg Suppositories (G&W) and Monistat-7
(Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

All eligible, enrolled patients: Treatment Group = G & W

	Baseline			1st Re-Visit				2nd Re-Visit			Mycol	Clin	
Subject	KOH	Cult	Symptoms	KOH	Cult	Symptoms	#Days	KOH	Cult	Symptoms	cure	cure	#Days
110	Positive	Positive	Mild	Negative	Negative	Mild	19	Negative	Negative	None	Yes	No	51
112	Positive	Positive	Mild	Negative	Negative	None	22	Negative	Positive	None	No	Yes	45
114	Positive	Positive	Moderate	Negative	Negative	None	22	Negative	Positive	None	No	Yes	43
117	Positive	Positive	Moderate	Positive	Positive	None	22	.	.	.	No	No	.
118	Positive	Positive	Severe	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	42
124	Positive	Positive	Moderate	Negative	Negative	Mild	18	Negative	Negative	Mild	Yes	No	43
127	Positive	Positive	Severe	Negative	Negative	None	15	Negative	Positive	None	No	Yes	36
128	Positive	Positive	Mild	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	51
141	Positive	Positive	Severe	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	43
146	Positive	Positive	Moderate	Negative	Negative	None	19	Negative	Negative	None	Yes	Yes	42
147	Positive	Positive	Severe	Negative	Negative	None	17	Negative	Positive	None	No	Yes	38
151	Positive	Positive	Moderate	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	36
152	Positive	Positive	Severe	Negative	Negative	None	20	Negative	Positive	None	No	Yes	41
153	Positive	Positive	Moderate	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	39
155	Positive	Positive	Moderate	Negative	Positive	None	19	.	.	.	No	Yes	40
158	Positive	Positive	Severe	Negative	Negative	None	18	Negative	Negative	None	Yes	Yes	39
160	Positive	Positive	Moderate	Negative	Negative	None	17	Negative	Negative	None	Yes	Yes	39
161	Positive	Positive	Moderate	Positive	Positive	None	18	.	.	.	No	No	.
162	Positive	Positive	Mild	Negative	Negative	None	13	Negative	Negative	None	Yes	Yes	37
165	Positive	Positive	Moderate	Negative	Negative	Mild	14	Negative	Negative	None	Yes	Yes	36
167	Positive	Positive	Severe	Negative	Negative	Mild	14	Negative	Negative	None	Yes	Yes	36
169	Positive	Positive	Mild	Positive	Positive	None	14	.	.	.	No	No	.
170	Positive	Positive	Mild	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	37

(3)

123

APPEARS THIS WAY
ON ORIGINAL

Project No. 901287

Comparison of Miconazole 100 mg Suppositories (G&W) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

All eligible, enrolled patients: Treatment Group = Ortho (52)

74-414

Subject	Baseline KOH	Baseline Cult	Baseline Symptoms	1st Re-Visit KOH	1st Re-Visit Cult	1st Re-Visit Symptoms	1st Re-Visit #Days	2nd Re-Visit KOH	2nd Re-Visit Cult	2nd Re-Visit Symptoms	Mycol cure	Clin cure	#Days
4	Positive	Positive	Mild	Negative	Negative	None	13	Negative	Negative	None	Yes	Yes	40
5	Positive	Positive	Moderate	Negative	Negative	None	18	Negative	Negative	Mild	Yes	No	40
8	Positive	Positive	Moderate	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	36
9	Positive	Positive	Mild	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	43
10	Positive	Positive	Severe	Negative	Positive	None	21	.	.	.	No	Yes	42
15	Positive	Positive	Mild	Negative	Negative	Mild	15	Negative	Negative	None	Yes	No	42
23	Positive	Positive	Mild	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	36
24	Positive	Positive	Mild	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	43
28	Positive	Positive	Moderate	Negative	Negative	None	13	Negative	Negative	None	Yes	Yes	42
31	Positive	Positive	Moderate	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	37
32	Positive	Positive	Mild	Negative	Negative	Mild	15	Negative	Negative	None	Yes	No	43
34	Positive	Positive	Moderate	Negative	Negative	None	20	Negative	Positive	None	No	Yes	49
35	Positive	Positive	Mild	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	37
37	Positive	Positive	Moderate	Negative	Negative	None	21	Negative	Positive	None	No	Yes	45
41	Positive	Positive	Mild	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	43
46	Positive	Positive	Severe	Negative	Negative	None	21	Negative	Positive	None	No	Yes	47
47	Positive	Positive	Severe	Negative	Negative	None	20	Negative	Negative	None	Yes	Yes	41
52	Positive	Positive	Moderate	Negative	Negative	None	19	Negative	Negative	None	Yes	Yes	41
53	Positive	Positive	Mild	Negative	Negative	None	20	Negative	Positive	None	No	Yes	42
56	Positive	Positive	Moderate	Negative	Negative	None	18	Negative	Negative	None	Yes	Yes	42
57	Positive	Positive	Mild	Negative	Negative	None	18	Negative	Negative	None	Yes	Yes	43
59	Positive	Positive	Mild	Negative	Negative	None	20	Negative	Negative	None	Yes	Yes	41
63	Positive	Positive	Moderate	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	44
66	Positive	Positive	Moderate	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	43
68	Positive	Positive	Moderate	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	39
75	Positive	Positive	Mild	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	30
76	Positive	Positive	Moderate	Negative	Positive	None	17	.	.	.	No	No	.
79	Positive	Positive	Mild	Negative	Negative	Mild	15	Negative	Negative	None	Yes	No	41
81	Positive	Positive	Severe	Negative	Negative	None	15	Negative	Positive	None	No	Yes	37
83	Positive	Positive	Moderate	Negative	Negative	None	19	Negative	Negative	None	Yes	Yes	40
85	Positive	Positive	Moderate	Negative	Negative	Mild	17	Negative	Negative	None	Yes	Yes	39
86	Positive	Positive	Moderate	Negative	Negative	None	17	Negative	Negative	None	Yes	Yes	39
89	Positive	Positive	Severe	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	39
91	Positive	Positive	Moderate	Negative	Negative	None	15	Negative	Negative	None	Yes	Yes	40
93	Positive	Positive	Moderate	Negative	Negative	Moderate	18	Positive	Negative	Moderate	No	No	39
99	Positive	Positive	Mild	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	49

(6)

3/6

APPEARS THIS WAY ON ORIGINAL

Comparison of Miconazole 100 mg Suppositories (G&W) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

All eligible, enrolled patients: Treatment Group = Ortho

Subject	Baseline KOH	Baseline Cult	Baseline Symptoms	1st Re-Visit KOH	1st Re-Visit Cult	1st Re-Visit Symptoms	1st Re-Visit #Days	2nd Re-Visit KOH	2nd Re-Visit Cult	2nd Re-Visit Symptoms	Mycol cure	Clin cure	#Days
103	Positive	Positive	Mild	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	48
105	Positive	Positive	Severe	Negative	Negative	None	22	Negative	Negative	Mild	Yes	No	52
108	Positive	Positive	Moderate	Negative	Negative	None	16	Negative	Positive	None	No	Yes	59
111	Positive	Positive	Moderate	Negative	Negative	None	22	Negative	Positive	None	No	Yes	50
116	Positive	Positive	Mild	Positive	Positive	None	21	.	.	.	No	No	
119	Positive	Positive	Severe	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	47
125	Positive	Positive	Severe	Negative	Negative	None	22	Negative	Negative	None	Yes	Yes	43
126	Positive	Positive	Severe	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	37
140	Positive	Positive	Moderate	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	43
143	Positive	Positive	Moderate	Negative	Negative	None	21	Negative	Negative	None	Yes	Yes	49
144	Positive	Positive	Moderate	Negative	Negative	Mild	14	Negative	Negative	None	Yes	Yes	42
145	Positive	Positive	Severe	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	36
148	Positive	Positive	Moderate	Negative	Negative	None	18	Negative	Negative	None	Yes	Yes	43
149	Positive	Positive	Severe	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	41
150	Positive	Positive	Severe	Negative	Negative	None	17	Negative	Negative	None	Yes	Yes	38
154	Positive	Positive	Severe	Negative	Negative	None	13	Negative	Negative	None	Yes	Yes	37
156	Positive	Positive	Severe	Negative	Negative	None	17	Negative	Negative	None	Yes	Yes	39
157	Positive	Positive	Severe	Negative	Negative	None	17	Positive	Positive	None	No	Yes	39
163	Positive	Positive	Mild	Negative	Negative	None	16	Negative	Negative	None	Yes	Yes	41
164	Positive	Positive	Mild	Negative	Negative	Mild	16	Positive	Positive	None	No	No	42
168	Positive	Positive	Severe	Negative	Negative	None	14	Negative	Negative	None	Yes	Yes	36

continued

List of All Patients by Investigator

Investigator	Patient
———	1
	2
———	33
	34 ✓
	35
	36 ✓
	37 ✓
	38
	39 ✓
	40
	49
	50
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	63 ✓
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	75 ✓
	76
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	78
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	80
———	93
	96
———	113
———	81
	82
	83
	84
	85
	86
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	88
	145
	146

Exclusion

(6)

Comparison of Miconazole 100 mg Suppositories (G&W) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

List of All Patients by Investigator

129
130
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Comparison of Miconazole 100 mg Suppositories (G&W) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

List of All Patients by Investigator

147
148
149
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
HFD-520 Division of Anti-infective Drug Prod		HFD-650 Division of Bioequivalence	
DATE: 7/96	IND NO.	NDA NO. N 74-414	TYPE OF DOCUMENT: Study Amendment
DATE OF DOCUMENT: 3/15/96			
NAME OF DRUG: Miconazole Nitrate Suppos	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: 45 Days
NAME OF FIRM: G & W Labs			

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ VAILABILITY STUDIES
- ☐ IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

For review by Dr. Julius Piver

Please review the enclosed additional information in reference to your earlier review of this application.

If possible please include a computer diskette, or the file name and LAN location so our reviewer can access the text. Thank you

Please return to the Generic Drugs Document Room -- Metro Park North II - Room E150
Deliver to Larry Galvin Room E118 -- Phone 4-2290 with any questions.

SIGNATURE OF REQUESTER 4/31	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

E L E C T R O N I C M A I L M E S S A G E

Date: 22-Feb-1996 08:46am EST
From: Mark Anderson
ANDERSONM
Dept: HFD-617 MPN2 113
Tel No: 301-594-0360 FAX 301-594-3839

TO: Robert West (WESTR)

CC: Jason Gross (GROSSJ)

Subject: FWD: Perrigo and G&W

Bob,

We issued the following letter to GW for their Miconazole Suppositories on 2/8/96:

Letter sent 2/8/96

ANDA 74-414

G&W Laboratories
Attention: Ronald Greenblatt
111 Coolidge Street
South Plainfield, NJ 07080-3895

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on October 8, 1993 and the amendments dated May 12, and September 5, 1995, for Miconazole Nitrate Vaginal Suppositories, 100 mg.

The Office of Generic Drugs in consultation with the Division of Anti-Infective Drug Products (HFD-520) has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The submission specified that there was a total of 117 evaluable subjects (60 in the G&W-group and 57 in the Ortho- group). The Agency reviewed the data associated with these subjects and concluded that of the 117 subjects evaluated by G&W, 21 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency alysis of the study there are 96 evaluable subjects, (51 in the G&W-group and in the Ortho- group). The following table summarizes the number of evaluable subjects (based on Agency analysis) per investigator.

Investigator	G&W	Ortho	Total
	12	11	23

	08		11		19	
	07		06		13	
		09		05		14
		03		00		03
	03		04		07	
		06		03		09
		02		04		06
	00		01		01	
		01		00		01
	00		00		00	
	00		00		00	
		00		00		00
Total	51		45		96	

2. The Agency only considered subjects for analysis who had resolution of all symptoms of disease at the second post- treatment visit (and subjects had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture at all visits to be therapeutic cures. Patents who were either a clinical failure and/or a mycological failure at either of the two follow-up visits were considered to be therapeutic failures. following tables summarizes the differences:

Group	Visit 2 Agency	[G&W]	Visit 3 Agency	[G&W]
Mycological Cure Rate				
G&W	45/51	[54/60]	39/51	[47/57]
Ortho	42/45	[54/57]	38/45	[44/55]
Clinical Cure Rate				
G&W	43/51	[55/60]	43/51	[52/57]
Ortho	44/45	[52/57]	41/45	[52/55]

Therapeutic Cure Rate	Visit 3 Agency	[G&W]
G&W	35/51	[40/60]
Ortho	37/45	[39/55]

3. The Agency evaluated the data based on 96 evaluable subjects as summarized above and concluded that:

a. The visit 3 data for "mycologic cure rates" fails to support the claim of equivalency due to failure to meet the lower bound of the 80-120% confidence interval.

b. The visit 2 data for "clinical cure rate" fails to support the im of equivalency due to failure to meet the lower bound of the 80-120% fidence interval.

c. The visit 3 data for "therapeutic cure rate" fails to support the claim of equivalency due to failure to meet the lower bound of the 80-120% confidence interval.

4. Agency analysis of the submitted data, demonstrates that the submitted study has failed to establish the bioequivalence of G&Ws test product to that of the reference listed drug Monistat-7 (Ortho).

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be considered major and be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

Office of Generic Drugs
Center for Drug Evaluation and Researchcc: Date

ANDA 74-414, Orig File, Dup File
DRAFT STM 01/31/96 X:\WPFILE\BIO\f74414D1.STU'Div File
Field Copy
HFD-615 PRickman
HFD-650 Gross, CST
HFD-520 J. Piver

BIO-LETTER INCOMPLETE

Endorsements:

J. Henderson
R. Patnaik
J. Gross

DRAFT	STM	01/31/96	X:\WPFILE\BIO\f74414D1.STU
DRAFT	JAG	01/31/96	X:\WPFILE\BIO\f74414D1.STU
FINAL PRINT	STM	02/07/96	X:\WPFILE\BIO\FINAL\F74414.STU

E L E C T R O N I C M A I L M E S S A G E

Date: 22-Feb-1996 09:29am EST
From: Robert West
WESTR
Dept: HFD-617 MPN2 113
Tel No: 301-594-0375 FAX 301-594-0180

TO: Anna Weikel (WEIKELA)
TO: Vilayat Sayeed (SAYEEDV)

CC: Paul Schwartz (SCHWARTZP)

Subject: FWD: Perrigo and G&W

If you haven't already done so, please issue a Not approvable letter to G&W referencing the bio letter issued 2/8/96. We need to get this off the books - pending at > 400 days.

See attached E-Mails

Thanks,

W.

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
1-16-96

NDA NUMBER

IND NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/SPONSOR
☒ FDA

MADE
☒ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME

FIRM NAME

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. Julius Piver
HFD-520

TELEPHONE NO.

ANDA	Firm	Product
73249	Copley	clotrimazole vaginal tablet 100 mg
74164	NMC	miconazole nitrate vaginal cream 2%
74366	G+W	micronized nitrate vaginal cream 2%
74395	Perrigo	miconazole nitrate vaginal suppository 100 mg
74414	G+W	miconazole nitrate vaginal suppository 100 mg

Dr. Julius Piver, HFD-520, DAIDP, did the consult reviews on all of the five ANDA's listed above. In some cases, Dr. Piver requested additional or reformatted data directly from the sponsor. Dr. Piver stated that, in all cases, he had received and reviewed all the additional data.

SIGNATURE
/S/

DIVISION
Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

DATE: December 6, 1995

TO: Director, Office Generic Drugs
HFD-632
7520 Standish Place
Rockville, Maryland 20855

FROM: Julius Piver, M.D.
Medical Officer, DAIDP, HFD-520

THROUGH: Renata Albrecht, M.D. /S/ 12/12/95
SMO, DAIDP, HFD-520

Mary Fanning, M.D., Ph.D /S/ 12/18/95
Director, DAIDP, HFD-520

SUBJECT: Consultation on ANDA 74-414

Please find attached to this memorandum, the medical consultation from HFD-520 which was requested. If there are any questions regarding this matter, please do not hesitate to contact the Division at 443-4110

Thank you for this consultation.

G & W Labs
Miconazole 1103
10/8/93 ✓ 1/1/95 rAM
5/12/95
9/5/95

LABELING REVIEW WORKSHEET

FIRM: F & W Laboratories, Inc. ANDA(s) 74-414
DRUG: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

LABELING OF THE LISTED DRUG

FIRM: AdvancedCare Products NDA#: 18-520
APPROVAL DATE: 2/8/95 REV.DATE: 9/93

CONTAINER LABELS

APPROVED COPY ON FILE? (Y) N DATE
USP CONTAINER/CLOSURE REQUIREMENTS: CRT, preserve in tight Containers

RECOMMENDED STORAGE STATEMENT:
ANDA: Same as NDA
NDA: Store at room temperature (15-30°C) (59-86°F). Avoid heat (over 30°C or 86°F).
OTHER KEY ISSUES: Firm has committed to print the established name and strength directly on the ~~—~~ when current stock is exhausted.

INSERT LABELING

PATENT & EXCLUSIVITY ISSUES: Ø

BIO ISSUES: No equivalency status was pending at the time of the ~~last~~ last chemistry review. Bio on consult to HFD-520.

ALL INACTIVE INGREDIENTS CITED? (Y) N
OTHER KEY ISSUES: Ø

APPROVAL SUMMARY

CONTAINER LABELS (SUBMISSION DATE): Satisfactory in FPL.
CARTON LABELING (SUBMISSION DATE): 3/8/95 submission Satisfactory in FPL 3/13/95
INSERT LABELING (SUBMISSION DATE): Submission Satisfactory in FPL 3/13/95
FORMULATION/SCORING SUMMARY: Submission Ø
COMMENTS OR FUTURE REVISIONS NEEDED: Ø

DATE: 3/14/95 REVIEWER: /S/ 3-21-95
SUPERVISOR: /S/ 3/27/95

OK 3/7/95 /S/

REV. 2/93; WP: WORK.293;JP

3/8/95

Ms. Frankel called this morning to say they she has prepared a Federal Express package containing 12 finished dosage form suppository products as a minor labeling amendment as detailed in the telecon to this application dated 2/9/95.

NDA NUMBER

ANDA NUMBER
74-414

TELECON/MEETING

INITIATED BY
- [X] APPLICANT/SPONSOR
- [ ] FDA

MADE
- [X] BY TELEPHONE
- [ ] IN PERSON

PRODUCT NAME
Miconazole Nitrate Vaginal Suppositories

FIRM NAME
G&W Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Frankel
Consultant in Regulatory Affairs

TELEPHONE NO.
(212) 755-2339

APPEARS THIS WAY
ON ORIGINAL

/S/

DIVISION
HFD-613

ORIGINATOR

REVIEW OF PROFESSIONAL LABELING #3

Original Amendment (Minor)

FPL

DATE OF REVIEW: January 25, 1995

ANDA #: 74-414

NAME OF FIRM: G & W Labs, Inc.

NAME OF DRUG: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

DATE OF SUBMISSION: January 3, 1995

COMMENTS:

Container:

We acknowledge your comments regarding your plans to deboss batch number and expiration date on unprinted premolded ——— containers on line. However, since the referenced listed drug container bears the proprietary name, we ask that you print the established name and strength of your drug product (Miconazole Nitrate Vaginal Suppository USP, 100 mg), accordingly. An abbreviation would be acceptable.

Carton:

Satisfactory

Insert:

Satisfactory

FOR THE RECORD:

a. The firm's Consultant in Regulatory Affairs, Carol Frankel, has been notified of the above request (see telecons dated 1/30/95, 2/8/95, and 2/9/95). The firm has ——— suppositories for which no labeling appears on the container ——— Ms. Frankel relayed that the firm will submit a minor labeling amendment which is to include:

- FPL container labels
- A physical sample of actual perforated, adhesive, container labels attached to the container.
- A commitment from the firm to directly imprint the container once equipment has been validated.

b. Insert labeling review is based on labeling submitted by Advanced Care Products, for Monistat® 7 Vaginal Suppositories approved October 8, 1992. Carton labeling review based on Monistat® 7 Vaginal Suppositories approved October 8, 1992.

c. Storage Recommendation:

Monistat® 7:	Store at room temperature (15-30°C)(59-86°F). Avoid heat (over 30°C or 86°F).
G & W:	Store at room temperature 15-30°C (59-86°F). Avoid heat over 30°C (86°F).
USP:	CRT, Preserve in tight containers.

d. Inactive Ingredients: hydrogenated vegetable oil base (both products).

Charlie Hoppes

cc: ANDA 74-414 /S/ 2/21/95 /S/ 2-21-95
HFD-613/CHOPPES/JGRACE/JPHILLIPS (no cc)
mpd/2/21/95; 74414.JAN
Review
final

/S/ 2/21/95

APPEARS THIS WAY
ON ORIGINAL

2/9/95

I called Ms. Frankel this morning to let her know that the firm's proposal of using perforated labels to place on existing stock is reasonable. I asked that she have the firm submit:

- FPL container labels
- A physical sample of actual container labels.
- A commitment from the firm to directly imprint the container label.

As a minor labeling amendment to this application.

Ms. Frankel will check with the firm this morning regarding a time frame to accomplish this.

2/9/95
Carol Frankel called back and said that the firm will commit to making the above changes within two weeks.

APPEARS THIS WAY ON ORIGINAL

/S/

NDA NUMBER
74-414

INC NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/SPONSOR
☐ FDA

MADE
☑ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Miconazole Nitrate Vaginal Suppositories USP

FIRM NAME
C & W Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Frankel
Consultant in Regulatory Affairs

TELEPHONE NO.
(212) 755-2339

DIVISION
HFD-613

ORIGINATOR

2/8/95

ANDA NUMBER
94-414

IND NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/SPONSOR
☒ FDA

MADE
☒ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Miconazole Nitrate Vaginal Suppositories, USP 100 mg

FIRM NAME
G & W Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Frankel
Consultant in Regulatory Affairs

TELEPHONE NO.
(212) 755-2339

I called Ms. Frankel this morning to let her know that the established name and strength will be required on the container shells for this product; that this decision is supported by the Branch Chief and by the Office of Compliance, Generic Drug Labeling; and that the approved generic products ~~and the listed drug~~ have this information (the listed drug is labeled MAVISTAT). I also let her know that we had requested this labeling in our letters of 3/2/94 and 10/21/94. I asked her to ask the firm to submit the labeling as a minor labeling amendment. She told me that she would relay this information to the firm.

2/8/95
Ms. Frankel called back to say that the firm is willing to use perforated stickers for the stock which has been packaged, ~~_____~~ suppositories. The sticker would allow one container label for each suppository.

SIGNATURE
/S/

LRB

DIVISION
HFD-603

ORIGINATOR

APPEARS THIS WAY
ON ORIGINAL

1/30/95

Regarding G&W's submission dated January 3 1995; the firm was requested to submit container labels for the referenced product. The listed drug Monistat® prints the proprietary name on the container we will request that G&W Labs print the established name of their product on the plastic suppository shell. Ms. Frankel will call the firm and return my call. Ms. Frankel contacted the firm and they will get back to her (she expects in a couple days) then let me know what their response is.

2/2/95

Ms. Frankel called to say that the responsible parties at the firm will not be available to ask about this until next week.

2/6/95

Ms. Frankel called. The firm can deboss the lot number and expiration date but not the established name on the containers. They have ~~—~~ shells that they would like to use before they validate new equipment which does have the capability to print on each shell. I told her that I would relay this information to my chief and call her back.

/S/

ANDA NUMBER
74-414

INC NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/SPONSOR
☒ FDA

MADE
☒ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Miconazole Nitrate Vaginal Suppositories USP, 100mg

FIRM NAME
G&W Laboratories, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Frankel
Consultant in Regulatory Affairs

TELEPHONE NO.
(212)755-2339

DIVISION
HFD-613

ORIGINATOR

APPEARS THIS WAY ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING #2

Original

DRAFT

DATE OF REVIEW: June 17, 1994

ANDA #: 74-414

NAME OF FIRM: G & W Labs, Inc.

NAME OF DRUG: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

DATE OF SUBMISSION: June 3, 1994

COMMENTS:

General:

We note that the established name of your product is, "Miconazole Nitrate Vaginal Suppositories USP, 100 mg". We ask that you revise your labeling to reflect this established name.

Container:

We note that you have planned to use plastic shells to encase the suppositories. We repeat our request that you submit the proposed labeling for these containers.

Carton (Back):

Revise statement appearing after, DIRECTIONS, to read:

Before using, read the enclosed brochure.

Insert:

1. WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?:

   a. Italicize "*candida*" where it appears.

   b. We acknowledge that we had previously requested the deletion of the following text in the first paragraph. However, this text <u>should</u> remain in place as follows:

      ...in the mouth, in the digestive tract, and...

   c. In the second paragraph, "...most often in some women...", (add the word "some").

   d. In the second sentence of the third paragraph, "One of the most serious...", ("most" rather than '

e. In the third sentence of the third paragraph revise as follows:

...vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you...

2. SYMPTOMS OF VAGINAL YEAST INFECTIONS:

a. First sentence, "...yeast infection. They can include:"

b. Following second bullet, "clumpy" rather than '~~~~'.

c. Third bullet, "...the vagina (vulvar irritation)."

3. WARNINGS:

a. We encourage the use of shading of this boxed section with a contrasting color to increase its prominence.

b. Place bullets in front of first two paragraphs; the paragraphs beginning, "This product..." and "**DO NOT USE...**".

c. Revise the second line following the second bullet as follows, "...**SIGNS AND SYMPTOMS.**", (delete the word ~~~~.

4. CONTENTS:

"**IMPORTANT**" rather than "TAMPER RESISTANT:" following the CONTENTS section. The entire IMPORTANT statement should appear in boldface type.

5. DIRECTIONS FOR USE:

Under step 3., lower case "m" and "n" in "miconazole nitrate".

6. FOR BEST RESULTS:

Under item 4., use "doctor" rather than " ~~~~~~~~ .

7. Revise your storage statement to be consistant in format with the storage statement appearing on your carton labeling.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then

prepare and submit draft container labels and final printed carton and insert labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

FOR THE RECORD:

a. Insert labeling review is based on labeling submitted by Advanced Care Products, for Monistat® 7 Vaginal Cream, rev. September 1993 (draft approved April 26, 1993) and on labeling for Monistat® 7 Vaginal Suppositories approved October 8, 1992. Carton labeling review based on Monistat® 7 Vaginal Suppositories approved October 8, 1992.

b. Storage Recommendation:

Monistat® 7: Store at room temperature (15-30°C)(59-86°F). Avoid heat (over 30°C or 86°F).

G & W: Store at room temperature 15-30°C (59-86°F). Avoid heat over 30°C (86°F).

USP: CRT, Preserve in tight containers.

c. Inactive Ingredients: hydrogenated vegetable oil base (both products).

Charlie Hoppes

cc: ANDA 74-414
HFD-613/CHoppes/MGonitzke (no cc)
njg/6/23/94/74414
Review
final

/S/ 6/27/94
/S/ 6/28/94

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	EER ID #
☒ Original ☐ Follow-Up ☐ FUR	1-6-96	574-0515	

REQUESTOR'S NAME	DIVISION	MAIL CODE
William Russell (CSO) / Vilayat Sayed M.D.	OED	HFD- 639

APPLICATION AND SUPPLEMENT NUMBER: G+W 74-414

BRAND NAME	ESTABLISHED NAME
Miconazole Nitrate	

DOSAGE AND STRENGTH	STERILE
Suppository 100mg	☐ YES ☒ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
SUP	

APPLICANT'S NAME: G+W Laboratories Inc

ADDRESS: 111 Coolidge St
S. Plainfield, NJ 07080-3895

COMMENTS:

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. Applicant	Manufacturing and Testing Facilities	— / NEC		
2.		DMF / CCS		
3.				
4.				
5. APPEARS THIS WAY ON ORIGINAL				

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

84

REVIEW OF PROFESSIONAL LABELING #1

Original

DRAFT

DATE OF REVIEW: February 10, 1994

ANDA #: 74-414

NAME OF FIRM: G & W Labs, Inc.

NAME OF DRUG: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

DATE OF SUBMISSION: December 6, 1993

COMMENTS:

Statements in the labeling of the reference listed drug reflecting warnings about HIV have not been incorporated into your labeling. The changes detailed below will include HIV warnings.

Container:

We note that you have planned to use plastic shells to encase the suppositories. We request that you submit the proposed labeling for these containers.

Carton:

1. General:

   a. The innovator provides for a printed seal which is placed on the end flaps as a tamper resistant feature. We believe that your product should have a similar feature.

   b. The innovator provides for the lot number and expiration date to be stamped into the end flap. We believe that you should provide similar labeling for your product.

2. Front Panel:

   The statement: "FULL PRESCRIPTION STRENGTH" should appear near the top of the front panel.

3. Back Panel:

   a. Throughout the labeling, replace '[redacted] with "doctor".

   b. "...you could not buy miconazole nitrate vaginal...", (lower case "m" and "n").

c. Remove active and inactive ingredient statements to a side panel and replace with: **"INDICATION:** For the treatment of vaginal yeast infections (candidiasis).".

d. Bold the section: **"FOR VAGINAL USE ONLY. DO NOT USE...".**

e. In the **WARNINGS** section, replace: **"IF THERE IS NO IMPROVEMENT...CONSULT YOUR PHYSICIAN.",** with:

IF YOU DO NOT IMPROVE IN 3 DAYS, OR IF YOU DO NOT GET WELL IN 7 DAYS, YOU MAY HAVE A CONDITION OTHER THAN A YEAST INFECTION. CONSULT YOUR DOCTOR. If your symptoms return within two months or if you have infections that do not clear up easily with proper treatment, consult your doctor. You could be pregnant or there could be a serious underlying medical cause for your infections, including diabetes or a damaged immune system (including damage from infection with HIV - the virus that causes AIDS). (PLEASE READ EDUCATIONAL BROCHURE FOUND WITHIN PACKAGE).

f. Let the sentence, **"Hydrogenated vegetable oil may...",** begin a new paragraph.

g. Delete the sentence, [redacted]".

h. Bulletize: **"Do not use tampons..."** and **"DO NOT USE IN GIRLS...".**

i. Replace: [redacted], with:

[redacted]

to be consistent with the request described above (Carton, item 1a).

j. Move statement of storage and company identification to a side panel.

4. Side Panel:

a. General:

The active and inactive ingredients, statement of storage conditions, company identification, and the below statement should appear on this panel.

b. Consistent with the request described in item 1b above and with the innovator's labeling, include the statement:

See end flap for lot number and expiration date.

c. Revise the storage condition statement to read:

Store at room temperature 15-30°C (59 -86°F). Avoid heat (over 30°C or 86°F).

Insert:

1. General:

   a. Throughout the insert, replace ' ——— ' with "doctor".

   b. Throughout the insert, use lower case "m" and "n" for the established name, miconazole nitrate.

2. Title:

   Replace ——————— with **"EDUCATIONAL BROCHURE"**.

3. Indication:

   Let the sentence: **"MICONAZOLE NITRATE VAGINAL SUPPOSITORIES ARE FOR THE TREATMENT..."**, begin a new paragraph.

4. What are vaginal yeast infections (Candidiasis)?:

   a. First paragraph:

   "...in the mouth, and in the vagina.", (delete "...———

   b. Second paragraph:

   "...often in some women who are pregnant, diabetic, taking antibiotics, taking birth control pills, or have a damaged immune system."

   c. Add the following text to begin a new paragraph after the second paragraph:

   Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV - the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections ——— If you may have been exposed to HIV and are now experiencing either frequently recurring vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection,

please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

IF YOU EXPERIENCE FREQUENT YEAST INFECTIONS (THEY RECUR WITHIN A TWO MONTH PERIOD) OR IF YOU HAVE YEAST INFECTIONS THAT DO NOT CLEAR UP EASILY WITH PROPER TREATMENT, YOU SHOULD SEE YOUR DOCTOR PROMPTLY TO DETERMINE THE CAUSE AND TO RECEIVE PROPER MEDICAL CARE.

5. Symptoms of vaginal yeast infections:

   a. "There are many signs and symptoms of a vaginal yeast infection."

   b. Delete '~~——~~' from the second symptom (i.e., A clumpy vaginal ...).

   c. Bold: **"NOTE:"**.

6. Warnings:

   a. Box the WARNINGS section of the insert with a contrasting color to further increase its prominence.

   b. Revise the first sentence to read:

      ...HAVE ANY OF THE SIGNS AND SYMPTOMS ~~————————~~ ALSO,...

   c. Capitalize all letters in the text:

      "DO NOT USE MICONAZOLE NITRATE...SMELLS BAD".

   d. In the fourth sentence:

      "...IF THEY OCCUR WHILE YOU ARE USING..."

   e. Indent:

      i) **"FEVER (ABOVE..."**
      ii) **"PAIN IN THE LOWER..."**
      iii) **"A VAGINAL DISCHARGE..."**

   f. After the bullet: "If there is no improvement...", add the following bullet:

      - If you may have been exposed to the human immunodeficiency virus (HIV, the virus that causes AIDS) and are now having recurrent vaginal infections, especially infections that don't clear up easily with proper treatment, see your doctor promptly to determine the cause of your symptoms and to receive proper medical care.

g. Delete the bullet:

[redacted]

7. Replace [redacted] with:

[redacted]

8. Directions for use:

Rotate the illustration in step two 180°.

9. Add the following section immediately after the **FOR BEST RESULTS** section:

IF YOU HAVE A QUESTION

Questions of a medical nature should be taken up with your doctor.

10. STORAGE; Revise to read:

Store at room temperature... (delete [redacted]

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit draft labeling.

FOR THE RECORD:

a. Labeling review is based on draft labeling submitted by the innovator, Advanced Care Products (reference listed drug: Monistat® 7), approved April 26, 1993.

b. Storage Recommendation:

Monistat® 7: Store at room temperature (15-30°C)(59-86°F). Avoid heat (over 30°C or 86°F).

G & W: Store at controlled room temperature 15-30°C (59-86°F). Avoid heat over 30°C (86°F).

c. Inactive Ingredients: hydrogenated vegetable oil base (both products).

Charlie Hoppes

DATE: December 6, 1995

TO: Director, Office Generic Drugs
HFD-632
7520 Standish Place
Rockville, Maryland 20855

FROM: Julius Piver, M.D.
Medical Officer, DAIDP, HFD-520

THROUGH: Renata Albrecht, M.D. /S/ 12/12/95
SMO, DAIDP, HFD-520

Mary Fanning, M.D., Ph.D. /S/ 12/18/95
Director, DAIDP, HFD-520

SUBJECT: Consultation on ANDA 74-414

Please find attached to this memorandum, the medical consultation from HFD-520 which was requested. If there are any questions regarding this matter, please do not hesitate to contact the Division at 443-4110

Thank you for this consultation.

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

pages of trade secret and/or confidential commercial information

October 20, 1993

On 10-12-93 Doc Room received an incomplete submission from G&W Labs. The box contained Vol. 7-11 - 5 copies (blue) and Vol. 3 & 4 - 2 copies (orange). I had an invoice from G&W Labs stating that 3 boxes were shipped UPS. The two lost boxes contained the following (box 1 - Vol. 1 - 2 copies (blue and red), Vol. 2 - 2 copies (blue & orange), Vol. 3-6 4 copies (blue), Box 3 - Vol. 5-11 - 7 copies orange. When boxes did not arrive went to mail room to check log book. Logged in G&W Labs for Doug Sporn, but not how many boxes.

10-19-93

Phoned Carol Frankel (Agent for G&W Labs) and inquired if all boxes had been shipped. She spoke to UPS, they confirmed that they had 3 signatures from mail room and that 3 boxes, 22 volumes) were delivered.

10-20-93

Mail room supervisor phoned me that the 2 boxes had been found. The boxes had been shipped out by accident from mail room and ended up at Shady Grove Post Office and then at Redland Post Office.

Jackets were delivered back to Doc Room and the received date given was 10-12-93. The name of the drug is Miconazole Nitrate Vaginal Suppositories 100 mg, and the ANDA # is 74-414.

Phoned Carol Frankel and informed her missing jackets have been found.

Prepared by Margo Bennett
Reviewed by Gordon Johnston /S/ 10/20/93

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-414

CORRESPONDENCE

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264

TREATMENT
N/A.C

March 21, 1997

Mr. Douglas Sporn , Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 74-414
Miconazole Nitrate Vaginal Suppositories , 100mg.

Dear Mr. Sporn:

Reference is made to a telephone conversation with Mr. Buccini along with Dr. Nashed and Dr. Schwartz on March 4, 1997 requesting additional information for the above referenced application. Attached hereto is the following:

1. Signed commitment to develop dissolution methods and specifications
2. Specifications for raw material , miconazole nitrate USP ——— , , which include limits for residual solvents ——————— at the same levels as the supplier
3. Specifications for release of the finished product, Miconazole Nitrate Vaginal Suppository , 100mg. which include tests and limits for Total Related Compounds of NMT — , and Content Uniformity
4. Specifications for stability which include tests and limits for Total Related Compounds of NMT ———
5. Test Method for Content Uniformity entitled ——— Assay Procedure for Miconazole Nitrate Vaginal Suppository, 100mg.

We trust that this information now completes this file.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
(212)755-2339 phone (212) 754-0704 fax

RECEIVED
MAR 2 4 1997

ANDA 74-414

G&W Laboratories, Inc.
Attention: Kripanath Borah, Ph.D.
111 Coolidge Street
South Plainfield NJ 07080

FEB - 6 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Miconazole Nitrate Vaginal Suppositories, 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. Please develop comparative dissolution methods (test *versus* reference) and specifications using 12 units. This data should be submitted to the Agency as soon as possible.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

G&W LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 • 908-753-2000 • Gen. Fax 908-753-9264 • Sales Fax 908-753-5174

May 16, 1996

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AA

RE: ANDA 74-414
MICONAZOLE NITRATE VAGINAL SUPPOSITORIES,
100 mg

Dear Mr. Sporn:

Reference is made to a fax received from Dr. Piver of the Division of Anti-Infective Drug Products dated May 1, 1996 requesting additional data. As per his request, attached hereto are the visit specific cure rates for mycological and clinical cures at visits 2 and 3 with and without the data from patient #75 included. It can be seen that in no instance is the confidence interval outside the ± 20% range; and inclusion or exclusion of patient #75 has no effect on the conclusion of equivalency of the two products.

Thank you for your kind cooperation and request your prompt attention to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-0704

RECEIVED
MAY 17 1996
GENERIC DRUGS

/S/ 5/16/96

G&W LABORATORIES, INC. 75 Years DIAMOND JUBILEE
Quality · Value · Innovation
Consistency Since 1919

G&W LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

March 15, 1996

Dr. Keith Chan, Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 74-414
Miconazole Nitrate Vaginal Suppositories, 100mg.

MAJOR AMENDMENT

Dear Dr. Chan:

Reference is made to your letter dated February 8, 1996 responsive to our ANDA submitted October 8, 1993 and amended May12 and September 5, 1995. We also refer to a memo from Dr. Jason Gross to Ms. Carol Frankel dated March 6, 1996 which provided patient details needed for our response. We are submitting herewith the response prepared by ——————— ——— the organization that directed the study.

We believe that this report satisfies the points raised in the letter. We have labeled this amendment as major as directed in your letter but we respectfully request that you consider reclassifying it as minor due to the extraordinary time invloved for this application. We acknowlege the recepit of your letter dated March 6, 1996 concerning this submission to the above referenced communications.

Thank you for your kind cooperation and prompt attention to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-0704

ANDA 74-414

Carol Frankel
Agent for: G & W Laboratories, Inc. MAR 6
333 East 57th Street
New York, NY 10022

Dear Madam:

This is in reference to your abbreviated new drug application dated October 8, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendments dated January 3, and March 8, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reason:

> We await your response to the letter of February 8, 1996, from the Division of Bioequivalence citing major deficiencies in your clinical study.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 3/5/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

FILE
74-414

3/6/96

The following page was FAXed to Carol Frankl on 3-6-96 to answer her phone inquiry

/S/

To: Carol Frankel:
Fax (212) 754-0704

From: Jason A. Gross, Pharm.D.
Project Manager
Division of Bioequivalence
Office of Generic Drugs
FDA

RE: Letter Dated 2/8/96
ANDA 74-414
G & W Laboratories
Miconazole Nitrate Vaginal Suppositories, 100 mg.

Ms Frankel as we discussed over the phone, item number 1 of the 2/8/96 letter specified the following:

> The submission specified that there was a total of 117 evaluable subjects (60 in the G&W-group and 57 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 117 subjects evaluated by G&W, 21 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 96 evaluable subjects, (51 in the G&W-group and 45 in the Ortho-group). The following table summarizes the number of evaluable subjects (based on Agency analysis) per investigator.

The 21 subjects that failed to return in the acceptable time frame are as follows:

	Subject number:	Total
For: [redacted]	34, 36, 37, 39, 63	5
[redacted]	75	1
[redacted]	06,90,92	3
[redacted]	143	1
[redacted]	46, 119, 128	3
[redacted]	99, 103, 105, 106 108, 110, 111, 112	8
		21

Thank You
JAG

/S/
3-6-96

ANDA 74-414

FEB -8 1996

G&W Laboratories
Attention: Ronald Greenblatt
111 Coolidge Street
South Plainfield, NJ 07080-3895

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on October 8, 1993 and the amendments dated May 12, and September 5, 1995, for Miconazole Nitrate Vaginal Suppositories, 100 mg.

The Office of Generic Drugs in consultation with the Division of Anti-Infective Drug Products (HFD-520) has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The submission specified that there was a total of 117 evaluable subjects (60 in the G&W-group and 57 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 117 subjects evaluated by G&W, 21 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 96 evaluable subjects, (51 in the G&W-group and 45 in the Ortho-group). The following table summarizes the number of evaluable subjects (based on Agency analysis) per investigator.

Investigator	G&W	Ortho	Total
[redacted]	12	11	23
[redacted]	08	11	19
[redacted]	07	06	13
[redacted]	09	05	14
[redacted]	03	00	03
[redacted]	03	04	07
[redacted]	06	03	09
[redacted]	02	04	06
[redacted]	00	01	01
[redacted]	01	00	01
[redacted]	00	00	00
[redacted]	00	00	00
[redacted]	00	00	00
Total	51	45	96

2. The Agency only considered subjects for analysis who had resolution of all symptoms of disease at the second post-treatment visit (and subjects had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture at all visits to be therapeutic cures. Patents who were either a clinical failure and/or a mycological failure at either of the two follow-up visits were considered to be therapeutic failures. The following tables summarizes the differences:

Group	Visit 2 Agency [G&W]		Visit 3 Agency [G&W]	
Mycological Cure Rate				
G&W	45/51	[54/60]	39/51	[47/57]
Ortho	42/45	[54/57]	38/45	[44/55]
Clinical Cure Rate				
G&W	43/51	[55/60]	43/51	[52/57]
Ortho	44/45	[52/57]	41/45	[52/55]

Therapeutic Cure Rate	Visit 3 Agency [G&W]	
G&W	35/51	[40/60]
Ortho	37/45	[39/55]

3. The Agency evaluated the data based on 96 evaluable subjects as summarized above and concluded that:

   a. The visit 3 data for "mycologic cure rates" fails to support the claim of equivalency due to failure to meet the lower bound of the 80-120% confidence interval.

   b. The visit 2 data for "clinical cure rate" fails to support the claim of equivalency due to failure to meet the lower bound of the 80-120% confidence interval.

   c. The visit 3 data for "therapeutic cure rate" fails to support the claim of equivalency due to failure to meet the lower bound of the 80-120% confidence interval.

4. Agency analysis of the submitted data, demonstrates that the submitted study has failed to establish the bioequivalence of G&Ws test product to that of the reference listed drug Monistat-7 (Ortho).

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be considered major and be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

APPEARS THIS WAY
ON ORIGINAL

ABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080-3895 • 908-753-2000 • Gen. Fax 908-753-9264 • Sales Fax 908-753-5174

Noted 9/18/95 /S/

September 5, 1995

Dr. Keith Chen, Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NEW CORRESP BIOAVAILABILITY
NC | 810

RE: ANDA 74-366
MICONAZOLE NITRATE VAGINAL CREAM 2%

ANDA 74-414
MICONAZOLE NITRATE VAGINAL SUPPOSITORIES 100 mg

Dear Dr. Chen:

Submitted herewith in duplicate are reformatted tables for the bioequivalence study of the ANDA 74-366 Miconazole Nitrate Vaginal Cream 2%. This is in compliance to a request from Dr. Julius S. Piver, Medical Officer with the Division of Anti-Infective Drug Products. The request was sent to us through Ms. Carol Frankel, Consultant in Regulatory Affairs for G & W Laboratories, Inc. by fax with sample charts.

We are also sending similarly reformulated tables for the bioequivalence study of ANDA 74-414 Miconazole Nitrate Vaginal Suppositories 100 mg which is also currently being reviewed by Dr. Piver.

Please transmit this data to Dr. Piver for his review and thank you for your cooperation on this matter.

Yours truly,
Ronald Greenblatt
Executive Vice President

RECEIVED
SEP 07 1995
GENERIC DRUGS

RG:peb

G&W LABORATORIES, INC. 75 Years DIAMOND JUBILEE
Quality-Value-Innovation Consistency Since 1919

/S/

Redacted 1

pages of trade secret and/or confidential commercial information

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9260

/S/

Noted -
9/7/95

NEW CORRESP BIOAVAILABILITY
NC/BIO

August 11, 1995

Mr. Douglas Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Dear Mr. Sporn:

We are writing this letter to bring to your attention the present status of two ANDA submissions which have been under review for two years. ANDA 74-366 was submitted for Miconazole Nitrate Vaginal Cream, 2% on May 27, 1993 and final printed labeling for this application on October 14, 1994. We also submitted ANDA 74-414 for Miconazole Nitrate Vaginal Suppositories, 100 mg. on October 8, 1993 and the last final printed labeling submission was made March 8, 1995. As you can see from this information the review of these applications is practically complete except for the bioequivalence sections which are under review in the Division of Anti-Infective Drug Products. I have been responding to data requests from the medical reviewer, Dr. Piver, since December 1994 for ANDA 74-366 and since May for ANDA 74-414. My last phone conversation with Dr. Piver was on August 8, 1995 during which he told me he was still working on ANDA 74-366 and had another application to review before he got to ANDA 74-414.

As you can see it is over two years since ANDA 74-366 was submitted and almost two years for ANDA 74-414. The OGD review work has essentially been finished for almost a year. It is not our experience for the bio study review to take such an unusually long time. The few companies that already received approval have the generic market to themselves. The price advantage for the consumer just is not realized in this situation. Future competitors, who performed the same quantity of work and invested the same large sums of money are being kept out of the market and hence keeping the price artificially high to the consumer. You will appreciate that in this era of high medical costs, that this seems to defeat the purpose for what the Waxman Hatch Law was supposed to create. We get the impression that your colleagues in the therapeutic review divisions are ignoring the generic requirements and sre handling these applications as new drugs. It seems as though the innovators are getting additional advantage even though their patents have expired.

RECEIVED

AUG 14 1995

GENERIC DRUGS

/S/

Is there something that OGD can do to rectify this situation? Please advise me if there is anything we can do to help speed up this process.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-0704

APPEARS THIS WAY
ON ORIGINAL

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

May 12, 1995

Dr. Keith Chen , Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Noted
/S/
9/7/95

Reference: ANDA 74-414
Miconazole Nitrate Vaginal Suppositories, 100 mg.

Dear Dr. Chen:

Submitted herewith in duplicate are reformatted tables for the bioequivalence study submitted with the above referenced ANDA. These have been changed to satisfy the request from Dr. Julius S. Piver , medical officer , with the Division of Anti-Infective Drug Products. He contacted us to explain his request and then sent sample charts.

We would appreciate it if you would transmit this data to Dr. Piver for his review. Thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N.Y. 10022
phone (212) 755-2339
fax (212) 754-0704

5-22-95

G&W LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

Container Labels Satisfactory - CMC PL
3/14/95 /S/

Patel /S/ 3.13.95

March 8, 1995

Rashmikant M. Patel, Ph.D., Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NIAM AMENDMENT

Reference: ANDA 74-414
Miconazole Nitrate Vaginal Suppositories,100mg.

Dear Dr. Patel:

Reference is made to our submission of final printed labeling dated January 3, 1995 and subsequent telephone conversations with Mr. Charles Hoppes of the agency. As a follow-up to the telephone calls enclosed herewith are 12 suppositories each with the added label "miconazole nitrate supp. 100 mg." on one end and the debossed lot number and expiration date "A-01/97" on the other end. These printed pressure sensitive labels will be used for the three batches of ——— suppositories each already manufactured in unprinted premolded — shells and the remaining ——— unprinted — shells in stock. When these are exhausted newly ordered — shells will come preprinted with this information. Appropriate copies will be submitted to this application at that time.

We trust this now completes this file but should you have any questions please feel free to contact me.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-07047

15 days /S/

Carton labeling and patient brochure satisfactory in PL.
See comment regarding container in review
1/5/95 /S/

Noted:
To Charlie Hoppes

/S/ 1/6/95

NDA
AMENDMENT
RPL

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

January 3, 1995

Rashmikant M. Patel, Ph.D., Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 74-414
Miconazole Nitrate Vaginal Suppositories USP, 100mg.

MINOR AMENDMENT

Dear Dr. Patel:

Reference is made to your letter dated Oct.21,1994 responsive to our ANDA dated October 8, 1993 and our amendment dated June 3, 1994. As suggested the labels and labeling have been revised as per your recommendations and therefore submitted herewith are 12 copies of final printed cartons and inserts. Please note that currently unprinted premolded —shells are used with the batch number and expiration date debossed on line.

Thank you for your kind cooperation and prompt attention to this matter. Should you have any further questions please feel free to contact me.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-0704

/S/ 1/4/95

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DATE: 10/26/94

TO: Carol Frankel

Attn:

PHONE: (212) 755-2339

FAX: (212) 754-0704

FROM: Mark Anderson

PHONE: (301) 594-0360

FAX: (301) 594-0180

NUMBER OF PAGES: 3
(Excluding Cover Sheet)

With this facsimile, the Office of Generic Drugs is providing you with a copy of a not approvable letter requesting your response in the form of a **MINOR AMENDMENT** for the following abbreviated new drug/antibiotic application:

(ANDA)/AADA NUMBER: 74-414 DATE OF LETTER: 10/21/94

NAME OF DRUG PRODUCT: Miconazole Nitrate Vaginal Suppos

SPECIAL INSTRUCTIONS:
Ms Frankel, you may have already received the "hard copy" of this letter by now but in case you haven't I am FAXing it to you.

/S/

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA 74-414

Carol Frankel
Agent for: G & W Laboratories, Inc.
333 East 57th Street
New York, NY 10022

OCT 21 1994

Dear Madam:

This is in reference to your abbreviated new drug application dated October 8, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendment dated June 3, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Labeling Deficiencies

General:

We note that the established name of your product is, "Miconazole Nitrate Vaginal Suppositories USP, 100 mg". We ask that you revise your labeling to reflect this established name.

Container:

We note that you have planned to use plastic shells to encase the suppositories. We repeat our request that you submit the proposed labeling for these containers.

Carton (Back):

Revise statement appearing after, DIRECTIONS, to read:

Before using, read the enclosed brochure.

Insert:

1. WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?:

   a. Italicize "*candida*" where it appears.

b. We acknowledge that we had previously requested the deletion of the following text in the first paragraph. However, this text <u>should</u> remain in place as follows:

...in the mouth, in the digestive tract, and...

c. In the second paragraph, "...most often in some women...", (add the word "some").

d. In the second sentence of the third paragraph, "One of the most serious...", ("most" rather than "~~~ .

e. Shorten the third sentence of the third paragraph and add a fourth sentence as follows:

...vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you...

2. SYMPTOMS OF VAGINAL YEAST INFECTIONS:

a. First sentence, "...yeast infection. They can include:"

b. Following second bullet, "clumpy" rather than ~~~ .

c. Third bullet, "...the vagina (vulvar irritation)."

3. WARNINGS:

a. We encourage the use of shading of this boxed section with a contrasting color to increase its prominence.

b. Place bullets in front of first two paragraphs; the paragraphs beginning, "This product..." and **"DO NOT USE..."**.

c. Revise the second line following the second bullet as follows, "...**SIGNS AND SYMPTOMS.**", (delete the word " ~~~ .

4. CONTENTS:

"IMPORTANT" rather than " ____________
following the CONTENTS section. The entire IMPORTANT statement should appear in boldface type.

5. DIRECTIONS FOR USE:

   Under step 3., lower case "m" and "n" in "miconazole nitrate".

6. FOR BEST RESULTS:

   Under item 4., use "doctor" rather than ____________ .

7. Revise your storage statement to be consistent in format with the storage statement appearing on your carton labeling.

Please revise your labels and labeling, then prepare and submit draft container labels and final printed carton and insert labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 10/21/94

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-414

OCT 21 1994

Carol Frankel
Agent for: G & W Laboratories, Inc.
333 East 57th Street
New York, NY 10022

Dear Madam:

This is in reference to your abbreviated new drug application dated October 8, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendment dated June 3, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Labeling Deficiencies

General:

We note that the established name of your product is, "Miconazole Nitrate Vaginal Suppositories USP, 100 mg". We ask that you revise your labeling to reflect this established name.

Container:

We note that you have planned to use plastic shells to encase the suppositories. We repeat our request that you submit the proposed labeling for these containers.

Carton (Back):

Revise statement appearing after, DIRECTIONS, to read:

Before using, read the enclosed brochure.

Insert:

1. WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?:

   a. Italicize "*candida*" where it appears.

b. We acknowledge that we had previously requested the deletion of the following text in the first paragraph. However, this text <u>should</u> remain in place as follows:

...in the mouth, in the digestive tract, and...

c. In the second paragraph, "...most often in some women...", (add the word "some").

d. In the second sentence of the third paragraph, "One of the most serious...", ("most" rather than ~~ ~~.

e. Shorten the third sentence of the third paragraph and add a fourth sentence as follows:

...vaginal yeast infections. **Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment.** If you...

2. SYMPTOMS OF VAGINAL YEAST INFECTIONS:

a. First sentence, "...yeast infection. They can include:"

b. Following second bullet, "clumpy" rather than ~~ ~~.

c. Third bullet, "...the vagina (vulvar irritation)."

3. WARNINGS:

a. We encourage the use of shading of this boxed section with a contrasting color to increase its prominence.

b. Place bullets in front of first two paragraphs; the paragraphs beginning, "This product..." and "**DO NOT USE...**".

c. Revise the second line following the second bullet as follows, "...**SIGNS AND SYMPTOMS.**", (delete the word ~~ ~~.

4. CONTENTS:

"**IMPORTANT**" rather than "_____" following the CONTENTS section. The entire IMPORTANT statement should appear in boldface type.

5. DIRECTIONS FOR USE:

   Under step 3., lower case "m" and "n" in "miconazole nitrate".

6. FOR BEST RESULTS:

   Under item 4., use "doctor" rather than "_____".

7. Revise your storage statement to be consistent in format with the storage statement appearing on your carton labeling.

Please revise your labels and labeling, then prepare and submit draft container labels and final printed carton and insert labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

MAJOR AMENDMENT

June 3, 1994

Rashmikant M. Patel, Ph.D., Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AC
Draft

Reference: ANDA 74-414
Miconazole Nitrate Vaginal
Suppositories USP, 100 mg

Dear Dr. Patel:

Reference is to your letter dated March 2, 1994 responsive to ANDA 74-414 for Miconazole Nitrate Vaginal Suppositories USP, 100 mg. The following are G & W Labs, Inc. responses to the deficiencies noted:

"A Chemistry Deficiencies

1.

"2.

RECEIVED
JUN 0 6 1994
GENERIC DRUGS

13 Jun 94

Redacted 3

pages of trade secret and/or confidential commercial information

ANDA 74-414

MAR 2 1994

Carol Frankel
Agent for: G & W Laboratories, Inc.
333 East 57th Street
New York, NY 10022

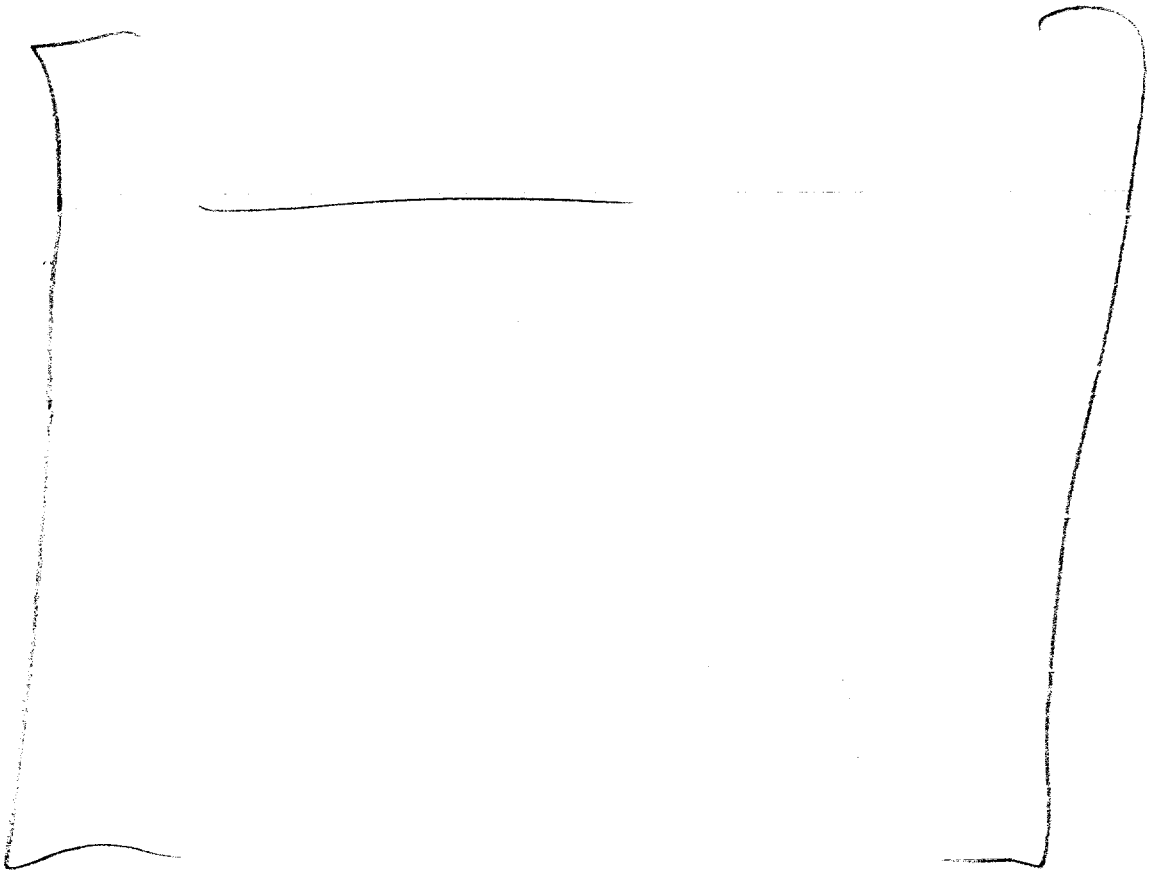
Dear Madam:

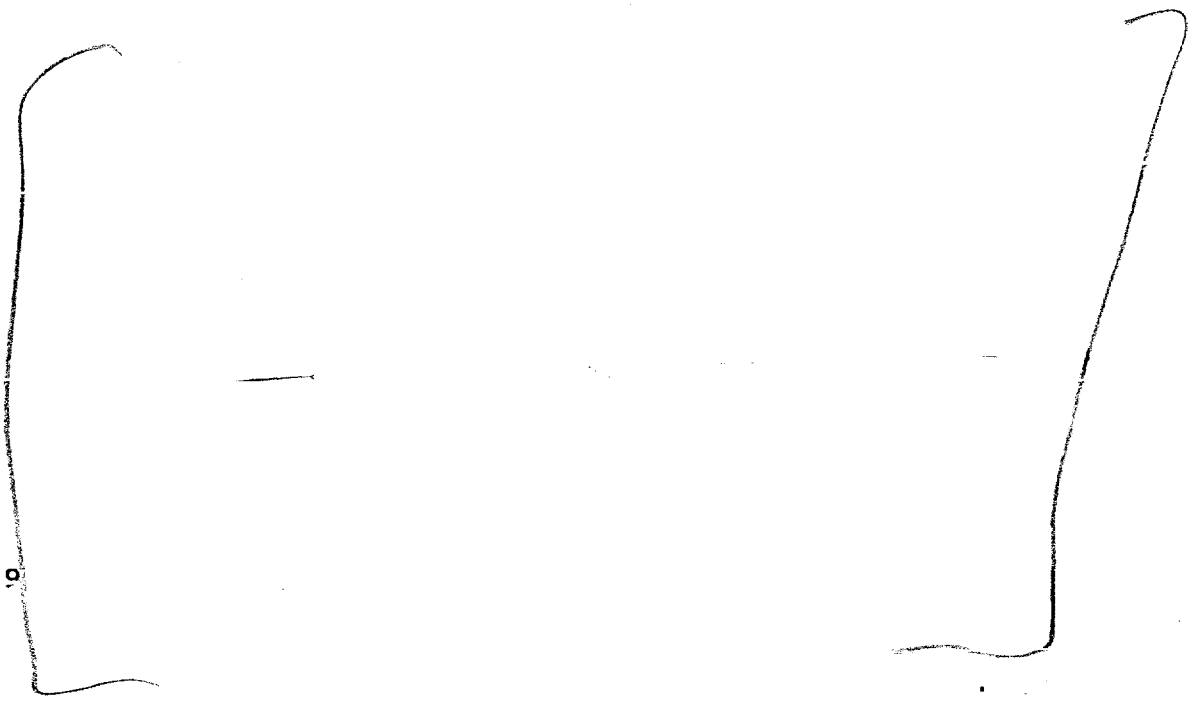
This is in reference to your abbreviated new drug application dated October 8, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendment dated December 6, 1993.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies





B. Labeling Deficiencies

Statements in the labeling of the reference listed drug reflecting warnings about HIV have not been incorporated into your labeling. The changes detailed below will include HIV warnings.

Container:

We note that you have planned to use plastic shells to encase the suppositories. We request that you submit the proposed labeling for these containers.

Carton:

1. General:

   a. The innovator provides for a printed seal which is placed on the end flaps as a tamper resistant feature. We believe that your product should have a similar feature.

   b. The innovator provides for the lot number and expiration date to be stamped into the end flap. We believe that you should provide similar labeling for your product.

2. Front Panel:

   The statement: "FULL PRESCRIPTION STRENGTH" should appear near the top of the front panel.

3. Back Panel:

   a. Throughout the labeling, replace [illegible] with "doctor".

   b. "...you could not buy miconazole nitrate vaginal...", (lower case "m" and "n").

   c. Remove active and inactive ingredient statements to a side panel and replace with: "**INDICATION:** For the treatment of vaginal yeast infections (candidiasis).".

   d. Bold the section: "**FOR VAGINAL USE ONLY. DO NOT USE...**".

   e. In the **WARNINGS** section, replace: "**IF THERE IS NO IMPROVEMENT...CONSULT YOUR** [illegible] ", with:

   [illegible]

   f. Let the sentence, "**Hydrogenated vegetable oil may...**", begin a new paragraph.

   g. Delete the sentence, [illegible] '.

h. Bulletize: **"Do not use tampons..." and "DO NOT USE IN GIRLS...".**

i. Replace: "[redacted], with:

IMPORTANT: [redacted]

to be consistent with the request described above (Carton, item 1a).

j. Move statement of storage and company identification to a side panel.

4. Side Panel:

a. General:

The active and inactive ingredients, statement of storage conditions, company identification, and the below statement should appear on this panel.

b. Consistent with the request described in item 1b above and with the innovator's labeling, include the statement:

See end flap for lot number and expiration date.

c. Revise the storage condition statement to read:

Store at room temperature 15-30°C (59 - 86°F). Avoid heat (over 30°C or 86°F).

Insert:

1. General:

a. Throughout the insert, replace [redacted]' with "doctor".

b. Throughout the insert, use lower case "m" and "n" for the established name, miconazole nitrate.

2. Title:

Replace [redacted] with **"EDUCATIONAL BROCHURE".**

C. rm did not make this change. We will not insist on this as only one form of tamper resistant packaging is required "
6/17/94

3. Indication:

Let the sentence: **"MICONAZOLE NITRATE VAGINAL SUPPOSITORIES ARE FOR THE TREATMENT..."**, begin a new paragraph.

4. What are vaginal yeast infections (Candidiasis)?:

a. First paragraph:

"...in the mouth, and in the vagina.", (delete "...in the digestive tract...").

b. Second paragraph:

"...often in some women who are pregnant, diabetic, taking antibiotics, taking birth control pills, or have a damaged immune system."

c. Add the following text to begin a new paragraph after the second paragraph:

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV - the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections

If you may have been exposed to HIV and are now experiencing either frequently recurring vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

IF YOU EXPERIENCE FREQUENT YEAST INFECTIONS (THEY RECUR WITHIN A TWO MONTH PERIOD) OR IF YOU HAVE YEAST INFECTIONS THAT DO NOT CLEAR UP EASILY

WITH PROPER TREATMENT, YOU SHOULD SEE YOUR DOCTOR PROMPTLY TO DETERMINE THE CAUSE AND TO RECEIVE PROPER MEDICAL CARE.

5. Symptoms of vaginal yeast infections:

   a. "There are many signs and symptoms of a vaginal yeast infection."

   b. Delete '~~—~~ ' from the second symptom (i.e., A clumpy vaginal ...).

   c. Bold: **"NOTE:"**.

6. Warnings:

   a. Box the WARNINGS section of the insert with a contrasting color to further increase its prominence.

   b. Revise the first sentence to read:

      ...HAVE ANY OF THE SIGNS AND SYMPTOMS ~~—————~~ ALSO,...

   c. Capitalize all letters in the text:

      "DO NOT USE MICONAZOLE NITRATE...SMELLS BAD".

   d. In the fourth sentence:

      "...IF THEY OCCUR WHILE YOU ARE USING..."

   e. Indent:

      i) **"FEVER (ABOVE..."**
      ii) **"PAIN IN THE LOWER..."**
      iii) **"A VAGINAL DISCHARGE..."**

   f. After the bullet: "If there is no improvement...", add the following bullet:

      - If you may have been exposed to the human immunodeficiency virus (HIV, the virus that causes AIDS) and are now having recurrent vaginal infections, especially infections that don't clear up easily with proper treatment, see your doctor promptly to determine the cause of

your symptoms and to receive proper medical care.

g. Delete the bullet:

[redacted]

7. Replace [redacted] with:

[redacted]

8. Directions for use:

Rotate the illustration in step two 180°.

9. Add the following section immediately after the **FOR BEST RESULTS** section:

IF YOU HAVE A QUESTION

Questions of a medical nature should be taken up with your doctor.

10. STORAGE; Revise to read:

Store at room temperature... (delete " [redacted] ").

Please revise your labels and labeling, then prepare and submit draft labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. All firms referenced in this application must be in compliance with cGMPs at the time of approval. An establishment inspection report has been requested from our Division of Manufacturing and Product Quality.

2. Your data submitted on the in-vivo bioequivalence study on Miconazole Nitrate Vaginal Suppositories 100 mg (Lot #0197-PB-13-A) comparing it to R. W. Johnson's Monistat® 7 Vaginal Suppositories (S100 mg (Lot #11D 317) is under review. You will be notified in a separate letter of any deficiencies identified in this portion of your application.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond

to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a major amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 2/28/94

Rashmikant M. Patel, Ph.D
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-414
ANDA #74-414/DUP/Division file
Field Copy
HFD-600/Reading file

Endorsements:

HFD-629/V.Sayeed/2-24-94 /S/ 2/28/94.

HFD-613/C.Hoppes/2-25-94 /S/ 2/28/94

HFD-619/P.Schwartz, Ph.D./2-24-94 /S/ 2-28-94

HFD-629/J.Dawson/CSO/2-24-94 /S/ 2/3/94

X:\Wpfile\Majors\Sayeed\74414L1.ORI
F/T by MM 2-25-94
Deficiency letter - Major Amendment

ANDA 74-414

Carol Frankel
Agent for: G&W Laboratories, Inc.
333 East 57th Street
New York, NY 10022

DEC 22 1993

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

DATE OF APPLICATION: October 8, 1993

DATE OF RECEIPT: October 12, 1993

DATE OF ACCEPTABLE FILING: December 7, 1993

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

/S/ 12/22/93

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA#74-414
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

/S/ 12/22/93

Endorsements:
HFD-615/Gordon Johnston, Chief/date/
HFD-615/PRickman, CSO/date/ /S/ 12/23/93
HFD-615/WRussell, CSO/date/ /S/ 12/15/93
HFD-629/PSchwartz PS 12/22/93
WP File\russell\74-414
F/T by bcw/12-16-93
ANDA Acknowledgement Letter!

/S/ 12/26/93

G&W
LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

505(b)(2) acceptable for filing 12/9/93 12/13/93

December 6, 1993

Draft Labeling
NDA ORIG AMENDMENT
N/AC

Douglas Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 74-414 Miconazole Nitrate
Vaginal Suppositories, 100 mg.

Dear Mr. Sporn:

Reference is made to a letter from Mr. Pollock dated November 16, 1993 refusing to file our ANDA submitted Oct. 8, 1993. Submitted herewith is the information requested in the letter.

Comparison of the inactive ingredients for the proposed drug product and the referenced listed drug.

Attached hereto is the comparison. Please note that they both contain a base of hydrogenated vegetable oil.

Differences between the proposed and reference listed drug labels and labeling.

In the ANDA submission we did note the differences between the proposed and reference drug labeling but on the introductory page to the section. In any event for your convenience we are submitting this herewith again with changes highlighted.

Signed certificate with an original signature concerning the submission of a true copy of the technical section to the field.

A signed certificate of authenticity is included with this submission.

We trust that this application can now be filed.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N.Y. 10022
(212) 755-2339

ANDA 74-414

NOV 16 1993

Carol Frankel
Agent for: G&W Laboratories, Inc.
333 East 57 St
New York, NY 10022

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You have failed to include a comparison of the inactive ingredients for the proposed drug product and the reference listed drug. Differences should be identified and characterized, and information provided demonstrating that the differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)].

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Please note that all differences between your proposed labels and labeling and the labels and labeling for the reference listed drug are required to be annotated and explained [21 CFR 314.94(a)(8)(iv)]. Please promptly provide this required information.

In addition, please include a signed certification with an original signature stating that the submitted field copy is a true copy of the technical section of the application [21 CFR 314.94(d)(5)].

Within 30 days of the date of this letter, you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell,R.Ph.
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 11/16/93

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-414
DUP/Jacket
DUP/Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-632/MBennett

Endorsements: HFD-632/Gordon Johnston, Chief/date /S/ 11/7/93
HFD-632/Reg Sup/date __/__/__
HFD-632/WRussell CSO/ 11/5/93 11/4/93
HFD-632/Chem Branch Chief/date 11/12/93 /S/ 11/9/93
WP File\B4:\Ref.fil\\74-414
F/T by hrw/date/11/04/93
AADA or ANDA REFUSE TO FILE!

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

G AND W
111 COOLIDGE ST
SOUTH PLAINFIELD NJ 07080

ANDA #: N074414

Dear Sir/Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG: Vaginal Suppositories USP, 100mg
MICONAZOLE NITRATE
Dosage Form: SUP Potency: 100 MG (VAGINAL) USP: Y

DATE OF APPLICATION: 08-OCT-93

DATE OF RECEIPT: 12-OCT-93

We will correspond with you further after we have had the opportunity to review the application.

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

/S/

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

G&W LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-

Refer to I/S 25 Oct 93

I/S 10/27/93

October 8, 1993

Douglas Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Dear Mr. Sporn:

Submitted herewith in duplicate is an Abbreviated New Drug Application (ANDA) for Miconazole Nitrate Suppository, 100mg. Our data is bound in 11 volumes per set but we understand that your filing system may break this down differently.

Volume I contains the chemistry, manufacturing and control parts of the application and volumes 2 through 11 contain the bioequivalency(clinical trial) report and supporting data.

Thank you for your kind cooperation in assigning a reference number to this application.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N.Y. 10022
(212) 755-2339