CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-586

Trade Name:	M-Zole 7 Dual Pack
Generic Name:	Miconazole Nitrate Cream USP, 2% And Miconazole Nitrate Vaginal Suppositories USP, 100 mg; Combination Package
Sponsor:	Alpharma, U.S. Pharmaceuticals Division
Approval Date:	July 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74-586

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-586

APPROVAL LETTER

ANDA 74-586

JUL 17 1997

Alpharma, U.S. Pharmaceuticals Division
Attention: Ronald Bynum
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated December 8, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg; Combination Package).

Reference is also made to your amendments dated June 13 and October 22, 1996; and April 30, May 21, June 20, and June 30, 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 Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg as presented in the combination package to be bioequivalent and, therefore, therapeutically equivalent to the respective components of the listed drug, Monistat® 7 Combination Pack, of Advanced Care Products.

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/ 7-17-97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-586

Final Printed Labeling

ALPHARMA™

NDC 0472-0729-19

Dual Pack

M-ZOLE 7

Miconazole Nitrate Vaginal Suppositories *and* External Vulvar Cream

IF THIS IS THE FIRST TIME YOU HAVE HAD VAGINAL OR VULVAR 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 AND CREAM AS DIRECTED.

INDICATIONS: For the treatment of vaginal yeast infections (candidiasis) and the relief of external vulvar itching and irritation associated with a yeast infection.

Before using, read the enclosed brochure.

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

DIRECTIONS: Suppositories–Insert one miconazole nitrate suppository high into the vagina at bedtime for seven nights in a row to treat vaginal yeast infection. Applicator and instructions are enclosed.

Cream–Squeeze a small amount of cream onto your finger and gently spread the cream onto the affected area of the vulva twice daily (morning and bedtime) for up to 7 days as needed to relieve external vulvar itching. **THE CREAM SHOULD NOT BE USED FOR VULVAR ITCHING DUE TO CAUSES OTHER THAN A YEAST INFECTION.**

WARNINGS: DO NOT USE M-ZOLE 7 DUAL PACK IF YOU HAVE ANY OF THE SIGNS AND SYMPTOMS LISTED BELOW. ALSO, IF THEY OCCUR WHILE USING M-ZOLE 7 DUAL PACK, 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 INSIDE PACKAGE).

Hydrogenated vegetable oil may weaken latex in condoms or 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 suppositories.

- **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 help or contact a poison control center immediately.**

IMPORTANT: BOTH END FLAPS OF THIS PACKAGE ARE SECURED WITH A PRINTED SEAL. DO NOT PURCHASE IF SEAL HAS BEEN EITHER REMOVED OR BROKEN.

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

See end flap for lot number and expiration date.

Miconazole Nitrate Vaginal Suppositories

ACTIVE INGREDIENT: miconazole nitrate (100 mg each suppository).

INACTIVE INGREDIENT: hydrogenated vegetable oil base.

Miconazole Nitrate External Vulvar Cream

ACTIVE INGREDIENT: miconazole nitrate 2%.

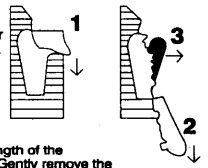
INACTIVE INGREDIENTS: benzoic acid, BHA, mineral oil, peglicol 5 oleate, pegoxol 7 stearate, purified water.

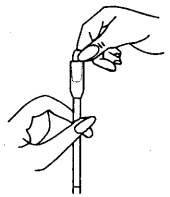
Manufactured by **Alpharma USPD Inc.**, Baltimore, MD 21244

0729029781 1478600-5303 BC2 VC400844

DIRECTIONS FOR USE
Miconazole Nitrate Vaginal Suppositories
Begin treatment at bedtime. Before going to bed:

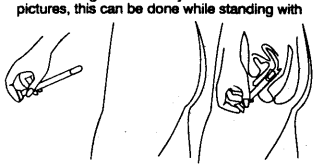
1 Break off suppository from the foil wrap. Tear the foil at the "V". Cut and peel the foil in a downward motion (1). Continue tearing downward to almost the full length of the suppository (2). Gently remove the suppository from the foil pocket (3).





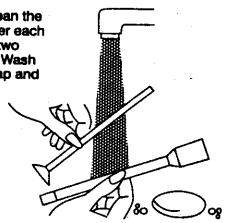
2 Place suppository in the top of the applicator as shown.

3 Hold the applicator containing the suppository by the opposite end from where the suppository is. Gently insert the applicator into the vagina as far as it will go comfortably. As shown in the pictures, this can be done while standing with



your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. Once you are ready, push the inside piece of the applicator in and place the suppository as far back in the vagina as possible. Then remove the applicator from the vagina. You should go to bed as soon as possible after inserting the suppository. This will keep leakage to a minimum. You may want to use deodorant-free mini-pads or pantyshields during the time that you are using Miconazole Nitrate Vaginal Suppositories. This is because the suppository can leak. DO NOT USE TAMPONS.

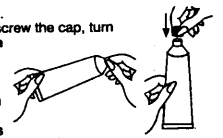
4 Be sure to clean the applicator after each use. Pull the two pieces apart. Wash them with soap and warm water. To rejoin, gently push the inside piece into the outside piece as far as it will go.



5 Repeat steps 1 through 4 before going to bed on each of the next six evenings.

Miconazole Nitrate External Vulvar Cream
Use the cream twice daily if needed as follows:

1 Open the tube. To do this, unscrew the cap, turn the cap upside down and place the cap in the end of the tube. Push down firmly until the seal is broken (as shown).



2 Squeeze a small amount of cream onto your finger.

3 Gently apply the cream onto the skin (vulva) that itches and is irritated.

4 Repeat steps 2 and 3 each morning and evening as needed.

ADVERSE REACTIONS (SIDE EFFECTS)
The following side effects have been reported with the use of the products in M-ZOLE 7 DUAL PACK: a temporary increase in burning, itching, and/or irritation when the suppository is inserted. Abdominal cramping, headaches, hives, and skin rash have also been reported. If any of these occur, stop using M-ZOLE 7 DUAL PACK and consult your doctor.

FOR BEST RESULTS
1. Be sure to use all of the suppositories even if your symptoms go away before you have used all the suppositories.
2. Use one suppository at bedtime for seven nights in a row, even during your menstrual period.
3. Wear cotton underwear.
4. If your partner has any penile itching, redness, or discomfort, he should consult his doctor and mention that you are treating yourself for a vaginal yeast infection.
5. Dry the outside vaginal area thoroughly after a shower, bath or swim. Change out of a wet bathing suit or damp workout clothes as soon as possible. A dry area is less likely to encourage the growth of yeast.
6. Wipe from front to rear (away from the vagina) after a bowel movement or urination.
7. Do not douche unless your doctor tells you to do so. Douching may disturb the vaginal bacterial balance.
8. Do not scratch if you can help it. Scratching can cause more irritation and can spread the infection.
9. Discuss with your doctor any medication you are now taking. Certain types of medication can make your vagina more prone to infection.

IF YOU HAVE A QUESTION
Questions of a medical nature should be taken up with your doctor.

ACTIVE INGREDIENTS
Miconazole Nitrate Vaginal Suppositories - miconazole nitrate (100 mg each suppository).
Miconazole Nitrate External Vulvar Cream - miconazole nitrate 2%.

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

Manufactured by
Alpharma USPD Inc.
Baltimore, MD 21244

Form No. 0729 I600-5303 BC-2 VC1301 Rev. 2/97

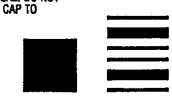
LABELING

MICONAZOLE NITRATE
EXTERNAL VULVAR CREAM, 2%

Net Wt. 0.32 oz (9 grams)

Relieves External Vulvar Itching & Irritation Associated With a Yeast Infection

FOR EXTERNAL VULVAR USE ONLY. DO NOT TAKE BY MOUTH OR USE IN EYES.
Keep out of reach of children. Before using, read the enclosed brochure for DIRECTIONS and WARNINGS.
IMPORTANT: TUBE OPENING IS COVERED BY A METAL TAMPER-EVIDENT SEAL. DO NOT USE IF SEAL HAS BEEN PUNCTURED OR CANNOT BE SEEN. **TO OPEN:** USE CAP TO PUNCTURE SEAL.
ACTIVE INGREDIENT: Miconazole Nitrate 2%.
See end of tube for lot number and expiration date.
Store at controlled room temperature 59°-86°F (15°-30°C).
Avoid heat (over 86°F or 30°C).
0730029781 VC081
Manufactured by **Alpharma USPD Inc.**, Baltimore, MD 21244



Alpharma USPD
M-Zole 7 Dual Pack
(Cream 2% and Suppositories 100 mg)
ANDA # 74-586

LABELING

NOT FOR ORAL USE • FOR VAGINAL USE ONLY
MICONAZOLE NITRATE
VAG. SUPP. USP 100 mg
Mfg. by: Alpharma USPD Inc., Baltimore, MD 21244
PF 700-5807

NOT FOR ORAL USE • FOR VAGINAL USE ONLY
MICONAZOLE NITRATE
VAG. SUPP. USP 100 mg
Mfg. by: Alpharma USPD Inc., Baltimore, MD 21244
PF 700-5807

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NOT FOR ORAL USE • FOR VAGINAL USE ONLY
MICONAZOLE NITRATE
VAG. SUPP. USP 100 mg
Mfg. by: Alpharma USPD Inc., Baltimore, MD 21244
PF 700-5807

ALPHARMA™
NDC 0472-0729-19

Dual Pack

M-ZOLE 7

Miconazole Nitrate Vaginal Suppositories *and* External Vulvar Cream

CURES MOST VAGINAL YEAST INFECTIONS

Relieves External Vulvar Itching &
Irritation Associated with a Yeast Infection

M-ZOLE 7

Miconazole Nitrate Vaginal Suppositories *and* External Vulvar Cream

ALPHARMA™
NDC 0472-0729-19

Dual Pack

M-ZOLE 7

Miconazole Nitrate Vaginal Suppositories *and* External Vulvar Cream

CURES MOST VAGINAL YEAST INFECTIONS

Relieves External Vulvar Itching &
Irritation Associated with a Yeast Infection

7 VAGINAL SUPPOSITORIES
plus EXTERNAL VULVAR CREAM

NET WT 0.32 OZ (9 GRAM) TUBE

ALPHARMA™

M-ZOLE 7

Miconazole Nitrate Vaginal Suppositories
and External Vulvar Cream

M-Zole 7 Dual Pack
(Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)
ANDA 74-586

OCT 1

EDUCATIONAL BROCHURE

M-ZOLE 7 COMBINATION PACK

MICONAZOLE NITRATE VAGINAL SUPPOSITORIES *and* EXTERNAL VULVAR CREAM

CURES MOST VAGINAL YEAST INFECTIONS AND RELIEVES ASSOCIATED ITCHING AND IRRITATION

RELIEVES EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION

INDICATIONS

For the treatment of vaginal yeast infections and the relief of external vulvar itching and irritation associated with a yeast infection.

If you have any or all of the symptoms of a vaginal yeast infection (vaginal itching, burning, discharge) accompanied by external vulvar itching and irritation and if at some time in the past your doctor has told you that these symptoms are due to a vaginal yeast infection, then M-ZOLE 7 COMBINATION PACK should work for you. If, however, you have never had these symptoms before, you should see your doctor before using M-ZOLE 7 COMBINATION PACK. **M-ZOLE 7 COMBINATION PACK IS FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS AND FOR THE RELIEF OF EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION. IT DOES NOT TREAT OTHER INFECTIONS OR EXTERNAL ITCHING AND IRRITATION DUE TO CAUSES OTHER THAN YEAST INFECTIONS. IT DOES 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". Some women also experience a yeast infection on the external skin (vulva) associated with the internal vaginal infection.

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 experiencing either frequently recurring vaginal yeast infections or, especially, 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.

SYMPTOMS OF VAGINAL YEAST INFECTIONS

There are many signs and symptoms of a vaginal 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 vaginal 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 M-ZOLE 7 COMBINATION PACK.

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast and in relieving vulvar itching and irritation associated with a yeast infection. Do not use in the eyes or take by mouth.
- **Do not use M-ZOLE 7 COMBINATION PACK if you have any of the following signs and symptoms. Also, if they occur while using M-ZOLE 7 COMBINATION PACK, STOP using these products 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. These suppositories contain hydrogenated vegetable oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using M-ZOLE 7 COMBINATION PACK.
- 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 these products 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

Miconazole Nitrate Vaginal Suppositories: Seven vaginal suppositories each containing 100 mg of miconazole nitrate. One plastic applicator.

Miconazole Nitrate External Vulvar Cream: One tube of cream for external vulvar use containing miconazole nitrate 2%.

IMPORTANT: THIS PRODUCT IS PROTECTED FROM TAMPERING IN SEVERAL WAYS. FIRST, BOTH END FLAPS OF THIS PACKAGE ARE SECURED WITH A PRINTED SEAL. DO NOT USE IF THE PACKAGE SEALS HAVE BEEN EITHER REMOVED OR BROKEN. SECOND, EACH MICONAZOLE NITRATE VAGINAL SUPPOSITORY IS INDIVIDUALLY WRAPPED. IF A SUPPOSITORY IS NOT WRAPPED OR THERE ARE SIGNS OF TAMPERING, DO NOT USE. THIRD, THE MICONAZOLE NITRATE EXTERNAL VULVAR CREAM TUBE OPENING IS COVERED BY A METAL TAMPER-EVIDENT SEAL. DO NOT USE IF THE METAL SEAL HAS BEEN PUNCTURED OR IF THE SEAL CANNOT BE SEEN. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

FINAL PRINTED LABELING
(INSERT)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-586

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 74-586

3. NAME AND ADDRESS OF APPLICANT

NMC Laboratories, Inc.
333 Cassell Drive
Suite 3500
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge, patent information has not been submitted to the FDA, and according to information published in the list of approved drug products 14th Ed., Monistat 7 Combination Pack is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

[redacted]

7. NONPROPRIETARY NAME

Miconazole Nitrate Vaginal Suppositories/
Miconazole Nitrate Cream

9. AMENDMENTS AND OTHER DATES:

Original 12/8/95
Amendment 12/19/95

10. PHARMACOLOGICAL CATEGORY

Treatment of vaginal yeast infections and the relief of external vulvar itching and irritation associated with a yeast infection.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's [redacted]

13. DOSAGE FORM

Vaginal suppositories/vaginal cream

14. POTENCY

100 mg/2%

15. CHEMICAL NAME AND STRUCTURE

1-[2,4-Dichloro-ß-[(2,4-dichlorobenzyl)oxy]
phenethyl]imidazole mononitrate

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 3/19/96

Supervisor: Paul Schwartz, Ph.D. 5/19/95

Redacted 11

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-586

3. NAME AND ADDRESS OF APPLICANT

Alpharma, U.S. Pharmaceuticals Division
333 Cassell Drive
Suite 3500
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge, patent information has not been submitted to the FDA, and according to information published in the list of approved drug products 14th Ed., Monistat 7 Combination Pack is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

[redacted]

7. NONPROPRIETARY NAME

Miconazole Nitrate Vaginal Suppositories/
Miconazole Nitrate Cream

9. AMENDMENTS AND OTHER DATES:

Original 12/8/95
Amendment 12/19/95
Amendment 6/13/96
Amendment 10/22/96
Amendment 4/30/97
Amendment 5/22/97
Amendment 6/20/97
Amendment 6/30/97

10. PHARMACOLOGICAL CATEGORY

Treatment of vaginal yeast infections and the relief of external vulvar itching and irritation associated with a yeast infection.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's ——————————

13. DOSAGE FORM

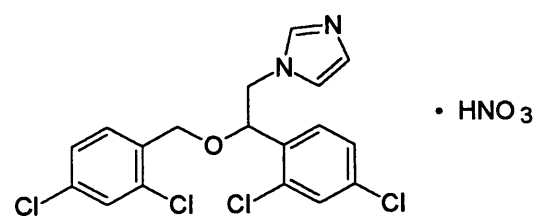
Vaginal suppositories/vaginal cream

14. POTENCY

100 mg/2%

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. USP 23, page 1026.



17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:
Nashed E. Nashed, Ph.D. 7/1/97
Supervisor: Paul Schwartz, Ph.D. 7/1/97

cc: ANDA 74-586
Division Copy
Field Copy

Endorsements:
HFD-627/N.Nashed, Ph.D./7-1-97 /S/ 7/1/97
HFD-627/P.Schwartz, Ph.D./7-1-97 /S/ 7/1/97
X:\NEW\FIRMSAM\ALPHARMA\LTRS&REV\74-586.2

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pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-586

BIOEQUIVALENCE REVIEW

ANDA 74-586

AUG 7 1996

NMC Laboratories, Inc.
Attention: Deborah Miran
333 Cassell Drive
Suite 3500
Baltimore MD 21224

Dear Madam:

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 Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package).

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

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/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 1 1996

ANDA: 74-586
Reviewer: A.P.Patel
File: x:\apatel\ 74586w.d94

NMC Laboratories
Glendale, NY
Submitted:
Dec. 8, 1994

Review of a waiver request

Introduction:

Miconazole is used in the treatment of vaginal yeast infections and relief from irritation associated with yeast infection.

Objective:

NMC Laboratories Inc. has applied for a waiver of clinical studies for their products, Miconazole 100 mg suppositories and Miconazole 2% Vaginal Cream packaged as _____. The reference listed product is Monistat 7 combination Pack manufactured by Ortho Pharmaceutical Corporation.

Comments:

1. The firm cites that Miconazole Nitrate Vaginal Suppositories, USP 100 mg submitted to FDA on Feb. 12, 1991 (ANDA# 73-507) and FDA approved it on Nov. 19, 1993.

2. Miconazole Nitrate External Vulvar Cream 2% has been submitted for review to the FDA on May 21, 1993 (ANDA# 74-164 and clinical study # 91021). The application at present is under review.

3. Formulations of suppositories and vaginal cream is shown in Table 1.

Recommendation:

The Division of Bioequivalence finds the application submitted by NMC Laboratories, Inc. for _____ incomplete. _____ contains Miconazole Nitrate Vaginal Suppositories, USP 100 mg (ANDA# 74-507) an approved product and Miconazole Nitrate External Vulvar Cream 2% (ANDA# 74-164) a product under review. The firm should be advised to submit this application for review pursuant to Miconazole Nitrate External Vulvar Cream 2% (ANDA# 74-164) approval.

The firm should be informed of the above recommendation.

/S/ 4/16/96

A.P.Patel
Division of Bioequivalence

FOR INTERNAL USE ONLY - NOT TO BE RELEASED THROUGH FOI

Table 1

Test Product vaginal Cream Formulation

INGREDIENT	AMOUNT/GRAM	% W/W
Miconazole nitrate, USP	0.02 g	2.0
mineral oil, NF		
pegoxol 7 stearate		
peglicol 5 oleate		
benzoic acid, USP		
purified water, USP		

Test Product Vaginal Suppository Formulation

INGREDIENT	AMOUNT/Unit
Miconazole nitrate, USP	100 mg
Vegetable Oil, Hyd.	
Vegetable Oil, Hyd.	

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-586 **SPONSOR:** NMC Laboratories

DRUG & DOSAGE FORM:

STRENGTH/(s): 100 mg suppositories / 2% Cream. N/A

TYPE OF STUDY: Single/Multiple N/A Fasting/Food

STUDY SITE: N/A

STUDY SUMMARY:

Waiver granted based on dual pack contains approved products.

DISSOLUTION: N/A

PRIMARY REVIEWER: /S/ **BRANCH:** 3

INITIAL: /S/ **DATE:** 12/20/96

BRANCH CHIEF: /S/ **BRANCH:** 3

INITIAL: /S/ **DATE:** 12/20/96

ACTING
DIRECTOR
DIVISION OF BIOEQUIVALENCE /S/

INITIAL: /S/ **DATE:** 12/20/96

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: **DATE:**

JUL 25 1996

ANDA: 74-586
Reviewer: A.P.Patel
File: x:\apatel\ 74586a.694

NMC Laboratories
Glendale, NY
Submitted:
June 13, 1996

Review of an Amendment

Background:

1. NMC Laboratories Inc. submitted for review of ANDA# 74-586 for a waiver of clinical studies for their products, Miconazole 100 mg suppositories (Approved ANDA# 74-507) and Miconazole 2% Vaginal Cream (under review ANDA# 74-164) packaged as [redacted]. The reference listed product is Monistat 7 combination Pack manufactured by Ortho Pharmaceutical Corporation.

2. ANDA# 74-586 was reviewed and found incomplete until Miconazole 2% Vaginal Cream (under review ANDA# 74-164) is deemed bioequivalent and approved.

Objective:

NMC Laboratories Inc.'s amendment for a waiver of clinical studies for their products, Miconazole 100 mg suppositories (Approved ANDA# 74-507) and Miconazole 2% Vaginal Cream (Approved ANDA# 74-164) packaged as [redacted] The reference listed product is Monistat 7 combination Pack manufactured by Ortho Pharmaceutical Corporation.

Comments:

1. Miconazole Nitrate Vaginal Suppositories, USP 100 mg submitted to FDA on Feb. 12, 1991 (ANDA# 74-507) and FDA approved it on Nov. 19, 1993.

2. Miconazole Nitrate External Vulvar Cream 2% had submitted for review to the FDA on May 21, 1993 (ANDA# 74-164 and clinical study # 91021)and FDA approved it on March 29, 1996.

3. The dual pack is a combination of approved products manufactured by NMC Laboratories and deemed to be bioequivalent to reference listed product Monistat 7 combination Pack manufactured by Ortho Pharmaceutical Corporation.

Deficiency: None

Recommendation:

The Division of Bioequivalence finds the application submitted by NMC Laboratories, Inc. for [redacted] acceptable. [redacted] contains an approved Miconazole Nitrate Vaginal Suppositories, USP 100 mg product (ANDA# 74-507) and an approved Miconazole Nitrate External Vulvar Cream 2% product (ANDA# 74-164). The Division of Bioequivalence deems [redacted] manufactured by NMC Laboratories, Inc. bioequivalent to the reference listed product Monistat 7 combination Pack manufactured by Ortho Pharmaceutical Corporation.

The firm should be informed of the above recommendation.

/S/ 7/24/96

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED R MHATRE
FT INITIALED R MHATRE /S/ Date: 7/26/96
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: /S/ Date: 7/25/96

Kieth Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA# 74-805 (Original, Duplicate), HFD 630 (OGD), HFD-600 (Hare), HFD-658 (R.M.Mhatre, A.P.Patel), Drug File, Division File.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-586

ADMINISTRATIVE DOCUMENTS

Contraception.

l Uses: An aesthetically
micid ly for use alone,
n o· ragm whenever
ıtra is desired.

)ccasional burning and/or
the vagina or penis have
l. In such cases, the medica-
)e discontinued and a phy-
ted as necessary. Not effec-
orally. Keep out of reach of
hen pregnancy is contra-
ıe contraceptive program
scussed with a health care

l Administration: When
ıjunction with a vaginal
Prior to insertion, put about
ul of GYNOL II Extra
ntraceptive Jelly into the
ome of the diaphragm and
ıll amount around the edge
ıgertip then insert.
)ortant to remember that if
)ccurs more than six hours
ın, or if repeated intercourse
an additional application of
:xtra Strength is necessary.
MOVE THE DIAPHRAGM,
more GYNOL II Extra
h the applicator provided in
ır package, being careful not
:he diaphragm. Remember,
lication of GYNOL II Extra
required each time inter-
eated, regardless of how lit-
; transpired since the dia-
been in place.
IT—For contraceptive effec-
diaphragm should remain
six hours after intercourse
e removed as soon as possi-
r. Continuous wearing of
m for more than 24 hours is
ended. Retention of the dia-
prolonged periods may en-
growth of certain bacteria in
tract. It has been suggested
ertain as yet unestablished
vergrowth of these bacteria
symptoms of toxic shock syn-
). For further information,
physician.

Administration: For use
lom or as a use-alone prod-
n applicatorful of GYNOL II
gth into the vagina as shown
tration. Intercourse should
ı one hour after GYNOL II
gth has been inserted. An
)plication must be used prior
litional act of intercourse.
ı of contraception must be
ınd every time intercourse
regardless of the time of the

ngredients: Lactic Acid,
)en, Povidone, Propylene
fied Water, Sodium Carboxy-
lose, Sorbic Acid, Sorbitol

n Product Identification
Section, page 418

MICATIN®
['mī-kə-tin]
Antifungal For Athlete's Foot

Description: An antifungal containing the active ingredient miconazole nitrate 2%, clinically proven to cure athlete's foot, jock itch and ringworm.

Indications: Athlete's foot (tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis).

Actions and Uses: Proven clinically effective in the treatment of athlete's foot (tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis). For effective relief of the itching, scaling, burning and discomfort that can accompany these conditions.

Directions: Cleanse skin with soap and water and dry thoroughly. Apply a thin layer of MICATIN over affected area morning and night or as directed by a doctor. For athlete's foot, pay special attention to the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily. Best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of this product and in jock itch with 2 weeks' use. If satisfactory results have not occurred within these times, consult a doctor or pharmacist. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails.
Do not use on children under 2 years of age except under the advice and supervision of a doctor. For external use only. If irritation occurs, or if there is no improvement within 4 weeks (for athlete's foot or ringworm) or within 2 weeks (for jock itch), discontinue use and consult a doctor or pharmacist. 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.

How Supplied:
MICATIN® Antifungal Cream is available in a 0.5 oz. tube and a 1.0 oz. tube.
MICATIN Antifungal Spray Powder is available in a 3.0 oz. aerosol can.
MICATIN Antifungal Deodorant Spray Powder is available in a 3.0 oz. aerosol can.
MICATIN Antifungal Powder is available in a 3.0 oz. plastic bottle.
MICATIN Antifungal Spray Liquid is available in a 3.5 oz. aerosol can.

Inactive Ingredients:
MICATIN Antifungal Cream: Benzoic Acid, BHA, Mineral Oil, Peglicol 5 Oleate, Pegoxol 7 Stearate, Purified Water.
MICATIN Antifungal Spray Powder: Alcohol, Propellant A-46, Sorbitan Sesquioleate, Stearalkonium Hectorite, Talc.
MICATIN Antifungal Deodorant Spray Powder: Alcohol, Propellant A-46, Talc, Stearalkonium Hectorite, Sorbitan Sesquioleate, Fragrance.
MICATIN Antifungal Powder: Talc.
MICATIN Antifungal Spray Liquid: Alcohol, Benzyl Alcohol, Cocamide DEA, Propellant A-46, Sorbitan Sesquioleate, Tocopherol.

Storage: Store at room temerature.
Shown in Product Identification Section, page 418

MICATIN®
['mī-kə-tin]
Antifungal For Jock Itch

Description: An antifungal containing the active ingredient miconazole nitrate 2%, clinically proven to cure jock itch.

Indications: Jock itch (tinea cruris).

Actions and Uses: Proven clinically effective in the treatment of jock itch (tinea cruris). For effective relief of the itching, scaling, burning and discomfort that can accompany this condition.

Directions: Cleanse skin with soap and water and dry thoroughly. Apply a thin layer of product over affected area morning and night or as directed by a doctor. Best results are usually obtained within 2 weeks' use of this product. If satisfactory results have not occurred within this time, consult a doctor or pharmacist. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails.

Warnings: Do not use on children under 2 years of age except under the advice and supervision of a doctor. For external use only. If irritation occurs, or if there is no improvement of jock itch within 2 weeks, discontinue use and consult a doctor or pharmacist. 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.

How Supplied:
MICATIN® Jock Itch Cream is available in a 0.5 oz. tube.
MICATIN Jock Itch Spray Powder is available in a 3.0 oz. aerosol can.

Inactive Ingredients:
MICATIN Jock Itch Cream: Benzoic Acid, BHA, Mineral Oil, Peglicol 5 Oleate, Pegoxol 7 Stearate, Purified Water.
MICATIN Jock Itch Spray Powder: Alcohol, Propellant A-46, Sorbitan Sesquioleate, Stearalkonium Hectorite, Talc.

Storage: Store at room temperature.

MONISTAT® 7
(miconazole nitrate)
Vaginal Cream, Suppositories

PRODUCT OVERVIEW

Key Facts: Monistat 7 is a vaginal antifungal. Monistat 7 is available in two forms: cream; and soft, emollient vaginal suppositories.

Major Uses: 1. For the treatment of **RECURRENT** vulvovaginal candidiasis (moniliasis) when the patient is treating herself, i.e. for women who have been diagnosed by a doctor in the past with vulvovaginal candidiasis, and who recognize the symptoms.
2. For the treatment of vulvovaginal candidiasis (moniliasis) for first-time sufferers **ONLY WHEN THE CONDITION IS DIAGNOSED BY A PHYSICIAN AND THE PHYSICIAN RECOMMENDATION CALLS FOR AN OTC PRODUCT.**

Safety Information:
- Do not use Monistat 7 if the following signs and symptoms are present. If they occur while using Monistat 7, STOP using the product and contact a doctor right away.
  —Fever (Above 100°F orally)
  —Pain in the lower abdomen, back or either shoulder
  —A vaginal discharge that smells bad
- If there is not improvement or if the infection worsens within three days, or complete relief is not felt within seven days, or your symptoms return within two months, then you may have something other than a yeast infection. You should consult your doctor.
- If your doctor has told you that you are sensitive or allergic to any Monistat product, do not use Monistat 7 without talking to your doctor first.
- 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.

PRODUCT INFORMATION

Active Ingredients: miconazole nitrate (vaginal cream, 2%; vaginal suppositories, 100 mg each)

Inactive Ingredients: Cream: benzoic acid, BHA, mineral oil, peglicol 5 oleate, pegoxol 7 stearate, purified water. Suppository: hydrogenated vegetable oil base.

Indications:
1. For the treatment of **RECURRENT** vulvovaginal candidiasis (moniliasis) when the patient is treating herself, i.e. for women who have been diagnosed by a doctor in the past with vulvovaginal candidiasis, and who recognize the symptoms.
2. For the treatment of vulvovaginal candidiasis (moniliasis) for first-time sufferers **ONLY WHEN THE CONDITION IS DIAGNOSED BY A PHYSICIAN AND THE PHYSICIAN RECOMMENDATION CALLS FOR AN OTC PRODUCT.**
As Monistat 7 is effective only for candidal vulvovaginitis, the physician diagnosis should be confirmed by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas* and *Haemophilus vaginalis* [*Gardnerella*]) should be ruled out by appropriate laboratory methods.

Actions: Monistat 7 exhibits fungicidal activity *in vitro* against the species of the genus *Candida*. The pharmacological mode of action is unknown.

Continued on next page

Printed by Joseph Buccine

Electronic Mail Message

Date: 11-Jul-1997 08:47am
From: Gordon Johnston
JOHNSTONG
Dept: HFD-601 MPN2 286
Tel No: 301-827-5845 FAX 301-594-0183

TO: Allen Rudman (RUDMANA)

CC: Nicholas Fleischer (FLEISCHERN)
CC: Paul Schwartz (SCHWARTZP)
CC: Joseph Buccine (BUCCINE)
Subject: ANDA 74-586

Allen,

You will likely receive an approval package for ANDA 74-586. The innovator reformulated its version of miconazole cream. In doing so, the innovator conducted a bioequivalence study with clinical endpoints to substantiate bioequivalence of the new formulation. Since a BE study shows equivalence between the old and new formulations of the RLD, OGD can approve an ANDA for the 'old' formulation.

This should resolve the policy and BE issue that had arisen over the formulation change by the innovator. If there are further questions, please feel free to discuss with Nick or myself.

Nick: Please add any additional comments if needed.

Gordon

CDER Establishment Evaluation Report
for July 16, 1997

Application: **ANDA 74586/000**
Stamp: **12-DEC-1994** Regulatory Due:
Applicant: **ALPHARMA USPD**
333 CASSELL DR STE 3500
BALTIMORE, MD 21224

Priority: Org Code: **600**
Action Goal: District Goal: **12-FEB-1996**
Brand Name:
Established Name: **MICONAZOLE NITRATE**
Generic Name:
Dosage Form: **CRM (CREAM)**
Strength: **100 MG/2%**

FDA Contacts:			
	J. BUCCINE	**(HFD-617)**	**301-827-5848 , Project Manager**
	N. NASHED	**(HFD-629)**	**301-827-5848 , Review Chemist**
	P. SCHWARTZ	**(HFD-629)**	**301-827-5848 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 28-MAY-1997 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 21-APR-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1053439**
ALPHARMA US PHARMACEUTICAL
1877 KAWAI ROAD
LINCOLNTON, NC 28092

DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 15-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Profile: **SUP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 07-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment: —

DMF No: —

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 20-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment: —

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**

Responsibilities:

CDER Establishment Evaluation Report
for July 16, 1997

Last Milestone: **OC RECOMMENDAT 11-DEC-1996** **FINISHED DOSAGE RELEASE TESTER**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 11-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 28-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 24-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No: Withdrawn - 6/30/97 amendment.

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 24-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

RECORD OF TELEPHONE CONVERSATION

At the request of Dr. Nashed, I called the firm and requested the following information:

* We could not find stability data for drug product using [redacted] as the [redacted] Please identify where these are located in the ANDA or withdraw [redacted]

* The [redacted] spec on page 802 calls for [redacted]. Results at 8 and 12 weeks says [redacted]. Please explain and justify.

* Provide all available room temperature stability data (e.g., 18 months for suppository)

* Provide recent COA for all DS manufacturers

Mr. Chris acknowledged.

x:\new\firmsam\alpharma\telecons\74586.003

cc:
ANDA
Division File
T-con Binder

DATE
6/17/97

ANDA NUMBER
74-586

IND NUMBER

TELECON

INITIATED BY FDA
Joe Buccine

PRODUCT NAME
[redacted]

FIRM NAME
ALPHARMA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
David Chris

TELEPHONE NUMBER
(410) 558-7250

SIGNATURE
Joseph Buccine

Paul FYI
FSI

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

Date: 14-Jan-1997 07:35pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: See Below

Subject: Miconazole 2%

Doug:

As I indicated in my 11-Jan-97 E-Mail, I spoke to Nick and he too did not think that generic firms would have to do a new BE study against the innovator's new formulation. He said that his Division would not support a position of requiring a generic applicant to perform a new BE study. As stated in Brad's E-Mail the new formulation met OGD's 90% CI. However it is understood that a new generic ANDA will have to go up against the new formulation once it is approved and marketed. Since the new NDA formulation is BE to the old formulation any new ANDA will be assumed to be TE to all other approved OTC miconazole drug products.

I think that this is now a dead issue and a meeting is not necessary. The next time you meet with Roger you may want to appraise him of the situation in case it comes up again in the future. Roger is aware that ODE's and OGD use a different CI i.e. 95% compared to 90%. It would be good if we had consistency within CDER i.e. everyone use 90%.

Don

Distribution:

TO: Doug Sporn (SPORND)

CC: Gordon Johnston (JOHNSTONG)
CC: Rabindra Patnaik (PATNAIK)
CC: Jerry Phillips (PHILLIPSJ)
CC: Mary Fanning (FANNINGM)
CC: Nicholas Fleischer (FLEISCHERN)

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

Date: 14-Jan-1997 05:49am EST
From: Gordon Johnston
JOHNSTONG
Dept: HFD-601 MPN2 286
Tel No: 301-594-0340 FAX 301-594-0183

TO: Rabindra Patnaik (PATNAIK)

CC: Doug Sporn (SPORND)
CC: Donald Hare (HARE)
CC: Jerry Phillips (PHILLIPSJ)
CC: Rabindra Patnaik (PATNAIK)

Subject: RE: Miconazole 2%

Rabi,

We will issue the approval letter for Taro's miconazole ANDA. There is no institutional decision at this time regarding the changes made to the RLD, that is, efficacy vs BE. IF CDER determines that the studies conducted by the RLD constitutes a change in the efficacy of the product, we will have to address the impact on the generics at that time. Options for the generics include an opportunity to conduct another BE study (and perhaps a reformulation) or BX labeling. These issues will have to be considered depending on how the RLD studies are ultimately defined.

Gordon

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

Date: 13-Jan-1997 06:59pm EST
From: Rabindra Patnaik
PATNAIK
Dept: HFD-651 MPN2 130
Tel No: 301-594-0350 FAX 301-594-0181

TO: Doug Sporn (SPORND)

CC: Gordon Johnston (JOHNSTONG)
CC: Donald Hare (HARE)
CC: Jerry Phillips (PHILLIPSJ)
CC: Rabindra Patnaik (PATNAIK)

Subject: Miconazole 2%

Doug:

Last couple of days I did not have access to e-mails. The story on Miconazole is very interesting. Based on the available information, I totally agree with Don. The generics are shown to be bioequivalent to the innovator's old formulation. If the innovator's new formulation is bioequivalent to its old formulation as per the current criteria, the generics will be deemed bioequivalent to the innovator's new formulation. I do not see any need for the generics to do additional clinical studies to stay on the market. Furthermore, most of the excipients in the topical products are "exception" excipients which a manufacturer can change due to various reasons. How many times in the past the innovators have made various postapproval changes in their formulation and have been deemed bioequivalent without actual bioequivalence testing. The major issue in my opinion is, whether the new formulation has changed the safety and efficacy of the drug product so that the two products are not bioequivalent clinically which as I understand, is probably not the case. If the clinical outcome are different, then there are merits for some consideration. I wonder, why at this time the innovator wanted to change its formulation. Many times we see "new improved" products on the market. Are these really clinically different than the old product? The clinical division will be able to answer that. We have to think carefully regarding these "new improved" products.

Today Roger signed off Taro's Miconazole application. The documents are with Gordie. Are we going wait till we resolve the current issue?

The office level sign off of Barr's Warfarin sodium has been done by Roger along with approval of 3 applications on Naproxen sodium (Perrigo, Novopharm, and Invamed). Gordie will probably inform you about all these.

Thanks,

Rabi.

[Action: If there is a meeting regarding miconazole, please let me know. I would like to attend that meeting] - Thanks,

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: 11-Jan-1997 03:50pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: Doug Sporn (SPORND)

CC: Rabindra Patnaik (PATNAIK)
CC: Jerry Phillips (PHILLIPSJ)

Subject: RE: FWD: Re: Miconazole 2%

Doug:

I will call Fleischer on Monday to see if he concurs with Brad. If he does not then a meeting may not be necessary in that OGD has all of the data that they need. If Nick agrees with Brad's assessment that new clinical studies are needed for already approved miconazole ANDAs then I will speak to Mary and we will arrange a meeting.

Don

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: 11-Jan-1997 03:16pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: Doug Sporn (SPORND)

CC: Rabindra Patnaik (PATNAIK)
CC: Jerry Phillips (PHILLIPSJ)

Subject: RE: FWD: Re: Miconazole 2%

Doug:

I don't agree with Brad's assessment in his 11-Jan-97 E-Mail that the generic firms will have to do another BE study with a clinical endpoint. The innovator's new drug product meets OGD 90% CI requirements and is therefore considered to be Therapeutic equivalent to the innovator's old formulation therefore the generics don't have to do a new study. (See my previous E-Mail on this issue.) The PK study with a 3-fold increase in BA was done for safety reason not efficacy.

s a possibility since we recommend but don't require the inactive ingredients to be the same between the test and reference topical product, the innovator may have had to change their product to meet the competition of a more cosmetically acceptable generic drug product.

As indicated previously I would recommend that we meet to discuss the issue.

Don

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: 11-Jan-1997 10:08am EST
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-2325

TO: See Below

Subject: Re: Miconazole 2%

In a message dated 12/30/96, Roger Williams wrote:

>Doug, Dave, Nick, Brad, Gordon:
>
>Just following up on an EMAIL from Nick indicating that the innovator for >miconazole 2% vaginal cream had changed the formulation to increase Cmax and
>AUC by 3 fold? Will this be a new NDA with different labeling? Is there a

>story here?
>
>Roger

In follow-up to this, Nick Fleischer responded on 12/30/96:

>The miconazole situation is a supplement to a NDA. The 3-fold increase in >systemic absorption most likely does not have an impact since IV doses of >this drug result in much higher levels.

>The only story which may unfold is how this will play out with already >approved generics or generics in the pipeline.

>Nick

(Sorry I'm so late in responding! Had to do some background research...)

Although alluded to, I believe we're discussing NDA 17-450 SCF-43 (chemistry supplement for "formulation revision") for MONISTAT 7 vaginal cream (2% miconazole). This application was submitted on 8/1/96 and has a review due date of 2/2/97.

The NDA holder, [redacted] and [redacted] In the applicant's cover letter, they state,

"...This change in formulation was in response to consumers' complaints of messiness and to recent [redacted]

Since activity (efficacy) of this vaginal product is dependent on local effect at the site of infection and not systemic absorption, bioequivalence must be shown using clinical end points. Therefore, a study was conducted under the IND...using the FDA Draft Guideline 'Performance of a

quivalence Study for Vaginal Antifungal Products', Feb. 1990. The results of this study indicated that the two formulations are equivalent..."

The only labeling claim change I can identify in the application is the addition of a "flag" on the carton stating:

According to the APPLICANT's data, the efficacy (therapeutic cure rate at the posttherapy followup visit) was as follows:

NEW FORMULATION (more viscous)	OLD FORMULATION (less viscous)
72/86 (83.7%)	67/94 (71.3%)

Using the corrected 95% CI, the limits are: {-0.7%, 26%}

Out of interest, using the corrected 90% CI (what if this was an OGD application), the limits are: {1.2%, 24%}

(Of interest, in the applicant's clinical summary section, they state: "The confidence intervals for the differences in...therapeutic cure rates between the MONISTAT 7 new formulation and the commercial formulation indicate that the two regimens are equivalent.")

Since the applicant is not claiming increased efficacy, we will focus our review on safety. Since systemic absorption is very small, we don't anticipate systemic safety concerns. Instead, we'll need to confirm that the increasing viscosity doesn't lead to increased local toxicity (e.g., irritation).

Certainly, if ACP was claiming increased efficacy, this would no longer be a Chemistry supplement.

Kudos to ACP for submitting this as a chemistry supplement (instead of an efficacy supplement) and getting a 6-month review out of us! Smart thinking on their part.

With regard to the impact of future OGD reviews, we anticipate that at some point there will need to be a regulatory transition period whereby the acceptable MONISTAT 7 control changes from the old formulation to the new formulation. Assuming NDA 17-450 SCF-43 is approved, at some point, generic drug firms will need to be told that they need to set up their studies comparing themselves to the new MONISTAT 7 formulation.

Enough said! :-)

Brad

cc: ribution:

TO: Roger Williams (WILLIAMSR)
TO: Doug Sporn (SPORND)

SUMMARY PACKAGE APPROVAL FOR 74-586

ANDA: 74-586

FIRM: Alpharma, U.S. Pharmaceuticals Division

DRUG: [redacted]

DOSAGE: Vaginal Suppositories/Vaginal Cream

STRENGTH: 100 mg/2%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 5/16/97

BIO STUDY/BIOEQUIVALENCE STATUS: Bio waiver was granted 7/26/96

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has submitted satisfactory three months accelerated stability data for the suppositories at 40°C/75%RH and 18 months room temperature at 25-30°C. The firm proposes a tentative expiration date of 18 months for the suppository product.
Three months satisfactory accelerated stability data at 40°C/75%RH and three months room temperature at 25-30°C for the cream were submitted.

LABELING REVIEW STATUS: The labeling is satisfactory 5/12/97

BATCH SIZES: The firm has submitted the master formula and manufacturing instruction and a copy of the executed batch lot # 700/580-L489, the batch size is [redacted] for suppositories. The intended production batch size is [redacted] for suppositories.
The firm has provided a copy of the exhibit batch of [redacted] for the cream. The intended production batch is [redacted]
The firm will be using same drug substance manufacturers [redacted] DMF [redacted], and [redacted] DMF [redacted] The DMF's are satisfactory. In addition the firm will be using same procedures and equipments.

COMMENTS: The application is APPROVABLE.

/S/ 7/1/97

Reviewer: Nashed E. Nashed, Ph.D. Date: 7/1/97

Supervisor: Paul Schwartz, Ph.D. /S/ 7/1/97

RECORD OF TELEPHONE CONVERSATION

Reference is made to the amendment dated June 20, 1997. Following review by Drs. Nashed, Schwartz and Rudman, the following comments were transmitted.

The response to comment #1 is unacceptable. Stability data for drug substance from ~~~~ supports the approval of product manufactured by ~~~~. However, ~~~~, is withdrawn. There are no data using ~~~~ at the proposed ~~~~ The ~~~~ data cannot be audited. Therefore, ~~~~ must be withdrawn as an ~~~~ at this time.

The ANDA lacks stability data to support expiry beyond 18 months for miconazole suppository. We recognize that the ANDA for the individual miconazole suppository drug product has a 24 month expiry; however, these data cannot be referenced. Each ANDA must stand alone. The issue is not scientific, but legal (i.e., regulatory fairness).

x:\new\firmsam\alpharma\telecons\74586.004
cc:
ANDA
Division File
T-con Binder

DATE
6/30/97

ANDA NUMBER
74-586

IND NUMBER

TELECON

INITIATED BY FDA
Joe Buccine

PRODUCT NAME
~~~~

FIRM NAME
ALPHARMA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
David Christ

TELEPHONE NUMBER
(410) 558-7250

SIGNATURE
Joseph Buccine

/S/ 6/30/97
~~~~

NASHED

ALPHARMA U.S. Pharmaceuticals Division

Facsimile Transmission

TO: Mr. Joseph Buccine
FDA, OGD, Div. Chemistry I

FAX NUMBER: (301) 594-0180
NO. OF PAGES: 23
(including cover)

FROM: David Christ /S/

DATE: June 20, 1997

SUBJECT: **M-Zole 7 Dual Pack**
Telephone Facsimile Amendment to ANDA #74-586

JRL

Attached please find a copy of subject (mailed today by overnight express).

1. Since [redacted] has been withdrawn, the data generated there cannot be used or reviewed (Also cannot be inspected) [redacted] is not acceptable for this ANDA

2. Since they only have 18 months [redacted] acceptable stability data [redacted] dissolution), expiration cannot exceed 18 months.

?

APPEARS THIS WAY
ON ORIGINAL

Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 • Fax: (410) 558-7262

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

Date: 02-Jan-1997 12:46pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: See Below

Subject: RE: FWD: miconazole 2% vaginal cream

Doug:

The reformulation of a RLD that does not meet our BE criteria is one of Roger's pet peeves.

You can be better and still be BE so long as the test product falls within the 80 to 125 range. If the test product was shown to have a better cure rate that was above the 125 ceiling I think that Roger would be a little upset.

Lidex and Lidex-E topical cream is an example of two drug products with different formulations with the same clinical response but the Lidex-E for some people is cosmetically more acceptable.

I would assume that the systemically availability study was done for toxicity reasons rather than efficacy. If the previous statement is correct then the clinicians made the decision that a three-fold higher BA of the reformulated miconazole vaginal cream did not present a safety problem.

In one respect this is not a problem since OTC products don't have a therapeutic equivalent rating however it is assumed that pharmaceutical equivalent OTC products are bioequivalent and therapeutic equivalent.

It may be worthwhile to meet with Nick to review the studies in more detail to head-off any possible attempt by the innovator to claim superiority over their generic counterparts.

Don

Distribution:

TO:	Doug Sporn	(SPORND)
CC:	Gordon Johnston	(JOHNSTONG)
CC:	Jerry Phillips	(PHILLIPSJ)
CC:	Mary Fanning	(FANNINGM)
CC:	Rita Hassall	(HASSALLR)
CC:	Nicholas Fleischer	(FLEISCHERN)

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

Date: 12-Aug-1995 01:37pm EDT
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: Gordon Johnston (JOHNSTON)

Subject: Options Surrounding Franchising

Gordie:

You requested I develop some options regarding franchising. You provided me a folder containing a response to a May 31, 1995 letter from Debbie Winkel that you and I developed, however the incoming letter was not there, and a controlled document assigned to Paul Schwartz concerning the same applications but with a somewhat different question. Since both of these documents are overdue I will provide options for these two issues, however I will review the history and describe some decisions that we made based upon our "franchising position".

HISTORY

I 'franchising" termed was coined to describe OGD's response to two petitions su..mitted in 1987 that requested a firm be allowed to reference data in another party's application as if it were their own to gain approval of their ANDA. Another way of describing this situation is that the first ANDA could be used as a drug master file by subsequent application holders. The second, third and fourth, etc., firms would not have to do an in vivo bioequivalence study to gain approval but would just have to do in vitro testing to meet the bioequivalence requirements. This concept was rejected by the OGD. The main reason for denying these petitions or requests was to prevent unqualified firms from entering the marketplace and to protect the integrity of the ANDA review process.

OGD developed a set of questions and answers to enforce this position in anticipation of various scenario's that could develop. During this early period the term that each "ANDA had to stand on its own" was developed.

Even though initially this policy was intended to rule out a second firm from referencing the data in another applicants ANDA it was subsequently expanded to prevent the same firm from using any data in another of its applications in support of an application approval.

IMPLEMENTATION OF POLICY

Gordie the following examples are some of the cases that I was involved in or I la..er became aware of. You had mention ——— in our conversation of Friday, t is one case that I was not involved in or am familiar with.

1. We did not permit, ——————— . no less, a waiver of the in vivo determination of bioequivalence for a ——————————————— even

t gh they were the contract manufacturer for an approved application. This was before the "Wiley-Williams" decision to waive the in vivo determination of bioequivalence if the inactive ingredients were Q and Q the same.

2. Subsidiaries of the innovator firm were required to do an in vivo bioequivalence studies if they desired to have their own ANDA rather than becoming a distributor. " Each ANDA had to stand on its own" policy.

3. ~~~~ requested permission to use an approved drug product from another firm to make a combination pack of vaginal cream and suppositories. Request was denied.

4. ~~~~~~~~~~~~~~~~~~ requests were turned down for (1) to permit a related company from using part of a lot from another application for their in vivo bioequivalence study (2) can the related company have a right of reference to CMC data in the innovator's application.

5. ~~~ request to permit one of their validation batches for etoposide injection to be used as an exhibit batch in another firms application was refused.

6. OGD has also said that two firm's could not cooperate in a three-way cross-over study and use the study for two ANDAs.

7 OGD has also that the same firm could not use a three-way study cross-over s y on two different polymorphs or a drug product that has two different

8. We have refused ~~~~ request to use the study from another firm in their corporation. They have appealed this decision to the Commissioner's Office.

NMC LABORATORIES REQUESTS

May 31, 1995 controlled correspondence.

In the draft letter we are permitting NMC to combined the drug product from two ANDAs into a combination drug product in a third ANDA. We are permitting the third ANDA to reference the in vivo bioequivalence studies and the CMC in the two ANDAs. However we are not permitting the firm to use one batch to make up two different lots for two ANDAs.

In the case of the bioequivalence study and the CMC data we are permitting one ANDA to use another ANDA as a drug master file and therefore we are bending our policy of "each ANDA having to stand on its own." I think that this is the correct decision in that it is not violating our initial reason for the "franchising" policy which has been defined as "each ANDA having to stand on its own" and that is to prevent incompetent or unqualified firms from going to market with a drug product that we may not have confidence in. The second r on why I think that this is a good decision is because of REGO. However the t letter does not permit the firm to split one manufacturing batch into two lots for two ANDAs.

Option 1 - Follow the draft outline.

Option 2 - Permit NMC to split a batch and use it in two ANDA's.

I prefer option 2 so as to be consistent of permitting a firm to reference all the data, not just part, in another ANDA so long they are the sole owner of the ANDA. The definitions of Batch and Lot in CFR 210.3 would not prevent OGD from accepting this option. I have not checked it out but if I recall the letter from NMC indicates that ODER divisions permit one batch to be used in two different applications as two different lots. However, I would not concur if the two ANDAs are owned by different firms even if they are in the same corporat etc. decisions.

June 7, 1995 controlled correspondence

NMC is planing a site change and they requested having to make exhibit batches only on the single drug product ANDAs. They don't want to make separate batches for the combo drug products.

Whether we grant NMC request will depend upon our response to the NMC May 31, 1995 letter.

Gordie lets try to get together ASAP because of the due date on these two NMC requests.

D

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

Date: 01-Nov-1995 02:43pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: Jason Gross (GROSSJ)

CC: William Rickman (RICKMAN)
CC: Jerry Phillips (PHILLIPSJ)

Subject: RE: Brain twister

Jason:

Do you lay awake at nite thinking of these unusual issues.

I agree with your response to question No. 1.

As you indicate two firms who have cooperative in doing a 3-Way cross over study would not be permitted to use that study in two ANDA's.

B[illegible]d upon some of our recent decisions with Barre, we stretch the policy of e[illegible] ANDA having to stand on its own when the same firm was involved. Your issue needs discussion but I like you think that this may be another instance in which we would permit a firm who held two ANDA's cross referencing information.

This same question was proposed for the two types of ranitidine. Could a 3-Way cross over study be used in two applications from the same firm. There was no resolution of this issue. It just went away.

One final thought and I don't mean to be rubbing salt in a wound but can we accept two NDA's from the same firm for the same drug product. Does an inactive ingredient make a different drug product?

Don

APPEARS THIS WAY
ON ORIGINAL

FILE IN ANDA 74-586

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

Date: 14-Jan-1997 07:35pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-0183

TO: See Below

Subject: Miconazole 2%

Doug:

As I indicated in my 11-Jan-97 E-Mail, I spoke to Nick and he too did not think that generic firms would have to do a new BE study against the innovator's new formulation. He said that his Division would not support a position of requiring a generic applicant to perform a new BE study. As stated in Brad's E-Mail the new formulation met OGD's 90% CI. However it is understood that a new generic ANDA will have to go up against the new formulation once it is approved and marketed. Since the new NDA formulation is BE to the old formulation any new ANDA will be assumed to be TE to all other approved OTC miconazole drug products.

I think that this is now a dead issue and a meeting is not necessary. The next time you meet with Roger you may want to appraise him of the situation in case it comes up again in the future. Roger is aware that ODE's and OGD use a different CI i.e. 95% compared to 90%. It would be good if we had consistency within CDER i.e. everyone use 90%.

Don

Distribution:

TO: Doug Sporn (SPORND)

CC: Gordon Johnston (JOHNSTONG)
CC: Rabindra Patnaik (PATNAIK)
CC: Jerry Phillips (PHILLIPSJ)
CC: Mary Fanning (FANNINGM)
CC: Nicholas Fleischer (FLEISCHERN)

RECORD OF TELEPHONE CONVERSATION

Reference was made to the amendment dated 4/30/97.

We request the following revised specifications for both the cream and suppositories:

For Drug Substance:

Individual known and unknown impurities NMT —

Total Impurities NMT —

For Release and Stability:

Individual known and unknown impurities NMT —

Total Impurities NMT —

Mr. Andolina will refer our request and respond.

I told him that resolution within the next 2-3 days could lead to an approval this month. A positive response should be submitted as a t-amendment provided by fax and f/u with a hard copy to the file.

Addendum Request: Please submit a committment to develop a dissolution test for the suppository. Mr. Andolina agreed.

x:\new\firmsam\alpharma\telecons\74586.002

cc:
ANDA
Division File
T-con Binder

DATE
5/19/97

ANDA NUMBER
74-586

IND NUMBER

TELECON

INITIATED BY FDA
Dr. Nashed
Joe Buccine

PRODUCT NAME
—

FIRM NAME
ALPHARMA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Vincent Andolina

TELEPHONE NUMBER
(410) 558-7250

SIGNATURE
Joseph Buccine
/S/ 5/19/97

CDER Establishment Evaluation Report
for May 19, 1997

Application: **ANDA 74586/000**
Stamp: **12-DEC-1994** Regulatory Due:
Applicant: **ALPHARMA USPD**
333 CASSELL DR STE 3500
BALTIMORE, MD 21224

Priority:
Action Goal:
Brand Name:
Established Name: **MICONAZOLE NITRATE**
Generic Name:
Dosage Form: **CRM (CREAM)**
Strength: **100 MG/2%**

Org Code: **600**
District Goal: **12-FEB-1996**

FDA Contacts:

J. BUCCINE	**(HFD-617)**	**301-827-5848**	**, Project Manager**
N. NASHED	**(HFD-629)**	**301-827-5848**	**, Review Chemist**
P. SCHWARTZ	**(HFD-629)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

WITHHOLD on 21-APR-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 16-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1053439**
ALPHARMA US PHARMACEUTICAL
1877 KAWAI ROAD
LINCOLNTON, NC 28092

DMF No:

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 15-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Profile: **SUP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 07-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No:

Responsibilities:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 20-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:

Responsibilities:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 11-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

CDER Establishment Evaluation Report
for May 19, 1997

Establishment: [redacted]

DMF No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 11-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment: [redacted]

DMF No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 24-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment: [redacted]

DMF No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 24-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

APPROVAL SUMMARY #2
(SUPERSEDES APPROVAL SUMMARY DATED NOV. 20, 1996)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-586 Date of Submission: April 30, 1997

Applicant's Name: Alpharma, U.S. Pharmaceuticals Division

Established Name: Miconazole Nitrate Vaginal Suppositories USP, 100 mg/Miconazole Nitrate Cream, 2%

Proprietary Name: M-Zole 7 Dual Pack

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels:

a. Suppository foil - Satisfactory as of April 30, 1997 submission

b. External Vulvar Cream (9 g) - Satisfactory as of April 30, 1997 submission

Carton Labeling:
Satisfactory as of April 30, 1997 submission

Patient Package Insert Labeling:
Satisfactory as of April 30, 1997 submission

Revisions needed post-approval:

Revise storage temperature recommendation to delete the use of "Controlled".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Monistat® 7 Combination Pack

NDA Number: 20-288

NDA Drug Name: Monistat® 7 Combination Pack

NDA Firm: Advanced Care Products

Date of Approval of NDA Insert and supplement: February 3, 1995

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:
NDAs 20-288 (Combination Pack), 17-450 (Cr), 18-520 (Supp)

Basis of Approval for the Carton Labeling: NDA 20-288

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	x		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	x		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.			x
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			x
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

noted /S/ 7/11/97

1. Please note that the cream formulation of the reference listed drug reformulated its product. The product now claims to be creamier.

2. Please ensure that the cap for the cream is designed to puncture the metal seal over the end of the tube. /S/ 7/11/97

FOR THE RECORD:

1. Labeling review based on Advanced Care Products' Monistat® 7 Combination Pack (20-288 - approved February 3, 1995).

   Advanced Care has reformulated its cream formulation so that it is now "creamier" and was approved March 21, 1997. Since this reformulation only effects the inactive ingredients, the labeling for this product will be based on the 1995 approved labeling.

2. In the acceptance to file letter, this product is referred to as "Miconazole Nitrate Cream USP, 2%, and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package). The labeling in this application refers to the cream as "Miconazole Nitrate External Vulvar Cream". This was allowed since it is not a proprietary name and its use provides consistency with the innovator's product.

3. M-ZOLE 7 Dual Pack was found acceptable by the LNC, with reservations, after a rejection of ' [redacted] . (See E-mails in file)

4. Packaging

   Monistat® is packaged as a 9 g tube of miconazole nitrate cream, 2% and 7 miconazole nitrate suppositories, 100 mg.

   Alpharma is proposing to package its suppositories in individual aluminum foil packets. Their cream will be packaged in white [redacted] tubes with the open end covered with a metal seal. The packaging configuration will be the same as Monistat's.

5. Labeling

   The "manufactured by" statement has changed. Alpharma is seeking approval, with this amendment, to manufacture both its cream and suppository products.

6. Inactive ingredients
The formulation used in this application is based on Monistat's old formulation. All inactives listed on the back panel of the carton labeling agree with those listed in the master batch formula submitted April 30, 1997.

All inactive ingredients have changed in Monistat's Vaginal Cream. It appears the new formulation no longer contains [redacted] Although this change was not made in the RLD's labeling, the CSO was notified of this discrepancy.

7. USP Issues

USP - Cream - Preserve in collapsible tubes or in tight containers.
Suppositories - Preserve in tight containers at controlled room temperature.

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

ANDA - Store at CRT 59°-86°F (15°-30°C). Avoid heat (over 86°F or 30°C). Since we asked firm to include "controlled" with its temperature range, we will wait until the first opportunity to ask them to delete it since it has no meaning with OTC products.

8. Bio - Review completed and found satisfactory August 7, 1996.

9. Patent/Exclusivity Issues - None pending.

10. This approval summary supersedes the one drafted November 20, 1996. An approval letter for this application was drafted in January, 1997, but does not appear to have been sent.

Approval Summary

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: November 20, 1996

ANDA Number: 74-586 Review Cycle: #2 (FPL)

Date of Submission: October 22, 1996

Applicant's Name [as seen on 356(h)]: Alpharma, U.S. Pharmaceuticals Division (Formerly NMC Laboratories, Inc.) -

Manufacturer's Name (If different than applicant):

NMC Laboratories, Inc. (cream)

Proprietary Name: M-ZOLE 7 DUAL PACK

Established Name: Miconazole Nitrate Vaginal Suppositories USP, 100 mg/Miconazole Nitrate Cream 2%

Reviewer: Lillie D. Golson

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

A. Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS:

a. Suppository foil - Satisfactory as of 10/22/96 submission

b. External Vulvar Cream (9 g) - Satisfactory as of 10/22/96 submission

CARTON LABELING:
Satisfactory as of October 22, 1996 submission

PATIENT PACKAGE INSERT LABELING:
Satisfactory as of October 22, 1996 submission

B. FUTURE REVISIONS

Revise to delete the use of "Controlled" for the temperature range.

C. BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Monistat® 7 Combination Pack

NDA Number: 20-288

NDA Drug Name: Monistat® 7 Combination Pack

NDA Firm: Advanced Care Products

Date of Approval of NDA Insert and supplement: February 3, 1995

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: 20-288

Basis of Approval for the Carton Labeling: 20-288

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? **In the acceptance to file letter, the product is referred to as "Miconazole Nitrate Cream USP, 2%, and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package). The labeling in this application refers to the cream as "Miconazole Nitrate External Vulvar Cream". This was allowed since it is not a proprietary name and its use provides consistency with the innovator's product.** - it is the same as Monistat-7 the RLD	X		
Is this product a USP item? If so, USP supplement in which verification was assured. **This is a combination of 2 products, each of which are USP. See USP 23, page 1027 for the cream and page 1028 for the vaginal suppository.**	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? **M-zole 7 Dual Pack approved by the L&N Committee (per John Grace)**		X	

Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **M-ZOLE 7 Dual Pack was approved, with reservations, after a rejection of "Miconazole Nitrate Dual Pack". (See attached E-mails)**	X		
PACKAGING - **Monistat® is packaged as a 9 g tube of miconazole nitrate cream, 2% and 7 miconazole nitrate suppositories, 100 mg.** **NMC is proposing to package its suppositories in individual aluminum foil packets. Their cream will be packaged in white ___ tubes with the open end covered with a metal seal. The packaging configuration will be the same as Monistat's.**			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? **The carton is needed to store the product components during course of treatment. The "Educational Brochure" should accompany the product.**			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
[redacted]			
Inactive Ingredients: (FTR: List p. # in application where inactives are listed) **Vol. 1.1, page 49**			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) **USP** **Cream - Preserve in collapsible tubes or in tight containers.** **Suppositories - Preserve in tight containers at controlled room temperature.** **NDA - Store at room temperature 15°-30°C (59°-86°F). Avoid heat (over 30°C or 86°F)** **ANDA - Same as RLD**			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? **However, firm has been asked to revise temperature storage to include "controlled".**		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) **Review completed and found satisfactory August 7, 1996**			
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **None pending.**			

NOTES/QUESTIONS TO THE CHEMIST:

Please ensure that the cap for the cream is so designed to puncture the metal seal over the end of the tube.

FOR THE RECORD:

1. Labeling review based on Advanced Care Products' Monistat® 7 Combination Pack approved February 3, 1995.

2. The newly proposed name "M-ZOLE 7 DUAL PACK" was submitted to the Labeling and Nomenclature Committee for review and comment and was approved with reservations (See attached E-Mails). Originally, the firm had submitted ~~which~~ which was rejected by the committee because it was determined to be an established name.

3. Alpharma now has ownership of NMC (See correspondence dated 8/30/96). Labeling now reflects their name. There is a qualifier on the carton indicating they are the distributor of this product.

4. At the earliest convenience, revise the storage temperature to delete "controlled" because this is not a desirable statement for OTC products.

5. All other FTR comments are contained in the Labeling Reviewer's Checklist.

/S/

Primary Reviewer

11/22/96
Date

/S/

Secondary Reviewer

11/22/96
Date

/S/

John Grace, Team Leader,
Labeling Review Branch

11/25/96
Date

cc: ANDA 74-586
Dup/Division File
HFD-613/LGolson/AVezza/JGrace (no cc)
njg/11/22/96/x:/new/firmsnz/nmc/ltrs&rev/74586apl.1
Review

RECORD OF TELEPHONE CONVERSATION/MEETING

Ron Bynum requested discussing some aspects of our NA letter requesting addition of specs and supplying data. They wish to commit to the specs and provide the data at a later date. Paul Schwartz discussed this request with him. Ron pointed out that most of [redacted] He also feels this product is well enough known that they shouldn't need to provide this data pre-approval. Paul feels the [redacted] question isn't an issue and, in our opinion, we need the revised specs pre-approval. Ron agreed to provide them.

DATE 8/9/96

AADA NUMBER 74-586

TELECON

INITIATED BY _ APPLICANT/ SPONSOR X FDA

MADE X BY TELE. _ IN PERSON

PRODUCT NAME [redacted]

FIRM NAME

NMC Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Ron Bynum

TELEPHONE NUMBER

(410)558-7250

SIGNATURE

/S/

William Russell,
Project Manager
Br IV

/S/

/S/ 8/9/96

APPEARS THIS WAY
ON ORIGINAL

FIRST GENERIC OF COMBINATION PACK

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: June 19, 1996

ANDA Number: 74-586 Review Cycle: #1 in Draft

Date of Submission: December 19, 1995

Applicant's Name [as seen on 356(h)]: NMC Laboratories, Inc.

Manufacturer's Name (If different than applicant):

NMC Laboratories, Inc. (cream)

Proprietary Name:

Established Name: Miconzole Nitrate Vaginal Suppositories USP, 100 mg
Miconazole Nitrate Cream USP, 2%

Reviewer: Lillie D. Golson

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

1. GENERAL COMMENT

   We have forwarded your proposed proprietary name of to the CDER Labeling and Nomenclature Committee for review and comment. We defer final comment on your labels and labeling pending resolution of this issue. We will notify you of their comments, when received.

2. CONTAINER

   a. Suppositories - Satisfactory in draft but see GENERAL COMMENT.

   b. External Vulvar Cream (9 g) (Front Panel)

      i. Enhance the prominence of the product's proprietary name, "MICONAZOLE NITRATE EXTERNAL VULVAR CREAM".

ii. Revise the storage recommendations to read, "Store at controlled room temperature..."

3. CARTON

a. See GENERAL COMMENT.

b. Tag Front and Front Panel

Revise to delete "ANTIFUNGAL VAGINAL SUPPOSITORIES *and* EXTERNAL VULVAR CREAM" appearing on the left side. The wording is redundant.

c. Tag Back (WARNINGS)

Revise the third bullet to delete the following "BAD"

d. Since each component of your drug product is statement for your signature line.

e. See comment (b)(ii) under CONTAINER.

4. INSERT (EDUCATIONAL BROCHURE)

a. Revise to delete " from the statement of identity to be consistent with the listed drug.

b. Revise the following statement and place it immediately below the statement of identity:

"CURES MOST VAGINAL YEAST INFECTIONS AND RELIEVES ASSOCIATED ITCHING AND IRRITATION"

c. SYMPTOMS OF VAGINAL YEAST INFECTIONS

Revise symptom #2 to read, "A clumpy, vaginal..." (delete '

d. WARNINGS

Please ensure that this section is boxed and shaded.

e. DIRECTIONS FOR USE

Revise sentence 2 of Direction #1 to read,

Tear the foil at the "V". Cut and peel... (make 2 sentences)

f. See comment (b)(ii) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in draft. Do not submit final printed labeling until you are notified that a decision regarding your proposed Proprietary Name has been reached by the CDER Labeling and Nomenclature Committee.

Changed or "x" deleted

~~Please revise your labels and labeling, as instructed above, and submit in final print.~~

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? In the acceptance to file letter, the product is referred to as "Miconazole Nitrate Cream USP, 2%, and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package). The labeling in this application refers to the cream as "Miconazole Nitrate External Vulvar Cream".	x		
Is this product a USP item? If so, USP supplement in which verification was assured. This is a combination of 2 products, each of which are USP. See USP 23, page 1027 for the cream and page 1028 for the vaginal suppository.	x		
Is this name different than that used in the Orange Book?		x	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	x		
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? Submitted 6/19/96.	x		

PACKAGING - Monistat® is packaged as a 9 g tube of miconazole nitrate cream, 2% and 7 miconazole nitrate suppositories, 100 mg. NMC is proposing to package its suppositories in individual aluminum foil packets. Their cream will be packaged in white [redacted] tubes with the open end covered with a metal seal. The packaging configuration will be the same as Monistat's.			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? The carton is needed to store the product components during course of treatment. The "Educational Brochure" should accompany the product.			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). However, have requested that NMC enhance the prominence of their proprietary name on the container label.		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) Labeling is in draft and the logo is not shown.			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?			
Inactive Ingredients: (FTR: List p. # in application where inactives are listed) Vol. 1.1, page 49			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	

Is there a discrepancy in ... ves ...ween DESCRIPTION and the composition statement?		x	
Has the term "other ingr... s" b... used to protect a trade secret? If so, is claim supported?		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) USP Cream - Preserve in collapsible tubes or in tight containers. Suppositories - Preserve in tight containers at controlled room temperature. NDA - Store at room temperature 15°-30°C (59°-86°F). Avoid heat (over 30°C or 86°F) ANDA - Same as RLD			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? However, firm has been asked to revise temperature storage to include "controlled".		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) Pending			
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. None pending.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. Labeling review based on Advanced Care Products' Monistat® 7 Combination Pack approved February 3, 1995.

2. [redacted]

for its prescription product. The proposed name has been submitted to the Labeling and Nomenclature Committee for review and comment.

3. On May 4, 1994, the M.O. requested that Advanced Care replace " ~~~~~ with "vaginal". NMC uses " ~~~~~ vaginal" a couple of times in their proposed labeling. Since CFR 201.61(b) indicates that the statement of identity should include the established name followed by "an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug", we have asked NMC to delete the use of the word " ~~~~~ to be consistent with the reference listed drug.

4. All other FTR comments are contained in the Labeling Reviewer's Checklist.

5. The Division of Bioequivalence recommended that NMC submit this application for review pursuant to the approval of Miconazole Nitrate External Vulvar Cream 2% (ANDA 74-164). That ANDA was approved March 29, 1996.

/S/ 7/1/96
Primary Reviewer Date

/S/ 7/2/96
Acting Team Leader, Date
Labeling Review Branch

cc: ANDA 74-586
Dup/Division File
njg/6/24/96/x:/new/firmsnz/nmc/ltrs&rev/74586na1.l
Review

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: January 2, 1996

FROM: William Russell, CSO, Regulatory Support Branch

TO: ANDA 74-586

SUBJ: Telecon

The field copy certification in the cover letter does not state "true" copy. It only says a field copy was sent. I spoke to Debbie Miran explaining the correct wording of the certification and asked that a revised one be sent.

1/16/96 - No response. I called Debbie Miran whose secretary said the pages were sent UPS on 1/3/96. After some searching, the Doc Control Room found a submission from this firm but it referenced the wrong NDA#. I asked Debbie to provide a new certification due to the wrong ANDA number, wrong document date, and wrong drug.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

NMC LABS
333 CASSELL DR STE 3500
BALTIMORE MD 21224

...A #: N074586

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:
MICONAZOLE NITRATE Dual Pack, 100mg/2% Suppositories & Cream
Dosage Form: ~~CRM~~ Potency: 100 MG/2% USP:

DATE OF APPLICATION: 08-DEC-94

DATE OF RECEIPT: 12-DEC-94

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 _____ 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/
HFD 629

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

BOTTOM PANEL

MONISTAT 7 Vaginal Suppositories:

Active Ingredient: miconazole nitrate (100 mg in each suppository)

Inactive Ingredients - hydrogenated vegetable oil base

MONISTAT External Vulvar Cream:

Active Ingredient: miconazole nitrate, 2%

Inactive Ingredients: benzoic acid, BHA, mineral oil, peglicol 5 oleate, pegoxol 7 stearate, purified water

Store at room temperature 15° to 30° C (59° to 86° F). Avoid heat (over 30°C or 86°F).
See end flap for lot number and expiration date.

Advanced Care Products
Ortho Pharmaceutical Corp.
Raritan, NJ 08869
 Made in U.S.A.

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

pages of trade secret and/or confidential commercial information

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS FOR HUMAN USE
(21 CFR 314.81)

DATE SUBMITTED
8/27/98

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Reverse of Part 1.

NOTE: This report is required by law *(21 USC 355; 21 CFR 314.81). Failure to report can result in withdrawal of approval of the New Drug Application.*

INSTRUCTIONS

Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

1. NDA OR ANDA NUMBER
N 7 4 5 8 6

2. Report No *(FDA Complete)*
Y- 0 0 1

APPLICANT NOTE
Reference NDA and Y numbers *(entered on Acknowledgement Copy)* in any subsequent correspondence regarding report.

4. APPLICANT
ALPHARMA, U.S. Pharmaceuticals Division

3. CFR SECTION NUMBER *(Antibiotic only)*

5. DRUG NAME
M-Zole 7 Dual Pack

6. TYPE OF REPORT *(Check one)*
☒ ANNUAL ☐ OTHER

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

8. PERIOD COVERED BY REPORT

FROM		TO	
YEAR	MONTH	YEAR	MONTH
97	07	98	07

Fold Line

REPORT INFORMATION REQUIRED *(See § 314.81 for description)*
9. *(Enter type of information attached under "Identification." If you have nothing to report, enter None.)*
(INFORMATION IN "9b" and "9c" IS ALWAYS REQUIRED.)

TYPE OF INFORMATION	IDENTIFICATION *(Volume No.(s)/Tab(s)/Page(s) of Report)*
a. SUMMARY OF SIGNIFICANT NEW INFORMATION	Green Header Page
b. DISTRIBUTION DATA	Green Header Page
c. LABELING *(Whether or not previously submitted)*	Green Header Page NAI /S/ 9/17/98
d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	Green Header Page
e. NONCLINICAL LABORATORY STUDIES	None
f. CLINICAL DATA	None
g. STATUS REPORT POST-MARKETING STUDIES	None
h. STATUS OF OPEN REGULATORY BUSINESS *(Optional)*	None

Fold Line

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL .. AGENT
Vincent Andolina
Manager, Regulatory Affairs

SIGNATURE
Vincent Andolina

APPLICANTS RETURN ADDRESS *(Type within the window envelope tic marks)*

Alpharma USPD Inc.
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

FDA USE ONLY

10. REPORT FILED IN NDA NUMBER
N 7 4 5 8 6

11. DATE OF RECEIPT

Received
AUG 31 1998
CENTER FOR DRUGS

FORM FDA 2252 (6/93) PREVIOUS EDITION IS OBSOLETE.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-586

CORRESPONDENCE

Redacted 2

pages of trade secret and/or confidential commercial information

ALPHARMA
U.S. Pharmaceuticals Division

June 30, 1997

NDA ORIG AMENDMENT
N/AM

Office of Generic Drugs
CDER, FDA
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, Alpharma herewith submits an amendment for M-Zole 7 Dual Pack, ANDA#74-586. Reference is made to Alpharma's amendments dated December 19, 1995, October 22, 1996; April 30, May 21, and June 20, 1997. Reference is also made to telephone conversations on June 30, 1997, between Mr. Joseph Buccine from the agency and David Christ of Alpharma. In these telephone conversations the agency requested two items from Alpharma.

The agency's comments are being restated and our response follows:

1. **The exhibit batch for the suppository does not meet all specifications under accelerated stability conditions (40°C/75% RH). Therefore the agency cannot approve at this time an expiration date of 24 months. An expiration date of 18 months would be acceptable.**

Alpharma proposes a tentative expiration date of 18 months for the suppository product based on the controlled room temperature stability data submitted as page 09 of the amendment dated June 20, 1997.

2. **The data submitted for [redacted] of the drug substance is for a batch [redacted] at the [redacted] Since this facility cannot be inspected by the agency, you must either submit data from the [redacted] facility or withdraw [redacted] as an**

JUL 02 1997

GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

Alpharma hereby withdraws [redacted] of the drug substance.

We trust that we have addressed the agency's concerns.

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to FDA's Atlanta district office.

Sincerely,
Alpharma

David Christ <for>

Ronald Bynum
Manager, Regulatory Affairs

RB:dc
cc: Atlanta District Office

PEARS THIS WAY
ON ORIGINAL

M-Zole 7 Dual Pack
Amendment to ANDA#74-586
Alpharma USPD Inc.

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION
June 30, 1997

Pursuant to 21 CFR 314.96(b), Alpharma, U.S. Pharmaceuticals Division certifies that the field copy is a true copy of the technical sections of this amendment, and the field copy has been sent to the Atlanta district office.

David Christ <for>
Ronald Bynum
Manager, Regulatory Affairs

6/30/97
Date

Enclosure

ALPHARMA
U.S. Pharmaceuticals Division

June 20, 1997

Office of Generic Drugs
CDER, FDA
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
/jm

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, Alpharma herewith submits an amendment for M-Zole 7 Dual Pack, ANDA#74-586. Reference is made to Alpharma's amendments dated December 19, 1995, October 22, 1996, and April 30, 1997. Reference is also made to a telephone conversation on June 17, 1997, between Mr. Joseph Buccine from the agency and David Christ of Alpharma. In these telephone conversations the agency requested four items from Alpharma.

The agency's comments are being restated and our response follows:

1. [redacted] is listed as an [redacted] but no supporting stability data was submitted. You must either submit data or withdraw as an [redacted]

We have enclosed as Attachment 1 accelerated (40°C/75% RH) and controlled room temperature (25-30°C) stability data through 12 months for 100 mg Miconazole Nitrate Vaginal Suppositories exhibit batch (Lot # 502010) [redacted] using drug substance from [redacted] These data were previously submitted as pages 255-256, and page 29 of the December 19, 1995, and October 22, 1996 amendments to this ANDA, respectively.

2. [redacted] Specification states " [redacted] 8 and 12 week stability data (Page 805) points indicate " [redacted] "." Please justify and explain.

Stability testing for the 100mg Miconazole Nitrate Vaginal Suppositories falls the [redacted]

RECEIVED
JUN 23 1997
GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

Testing specification at 40°C and 75% relative humidity. As explained on the memo on page 806 of the April 30, 1997, amendment, [redacted] is not a stability

[redacted]

3. Please provide available room temperature data for the suppository.

We have enclosed as Attachment 2 updated stability data through 18 months for the 100 mg Miconazole Nitrate Vaginal Suppositories exhibit batch (Lot No. L50989).

4. Please supply recent [redacted]

[redacted]

We trust that we have addressed the agency's concerns.

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to FDA's Atlanta district office.

Sincerely,
Alpharma

David Christ <for>

Ronald Bynum
Manager, Regulatory Affairs

RB:dc
cc: Atlanta District Office

M-Zole 7 Dual Pack
Amendment to ANDA#74-586
Alpharma USPD Inc.

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION
June 20, 1997

Pursuant to 21 CFR 314.96(b), Alpharma, U.S. Pharmaceuticals Division certifies that the field copy is a true copy of the technical sections of this amendment, and the field copy has been sent to the Atlanta district office.

David Child <for>
Ronald Bynum
Manager, Regulatory Affairs

6/20/97
Date

Enclosure

APPEARS THIS WAY
ON ORIGINAL

ALPHARMA
U.S. Pharmaceuticals Division

May 21, 1997

Office of Generic Drugs
CDER, FDA
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

N/AM
AMENDMENT

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, Alpharma herewith submits an amendment for M-Zole 7 Dual Pack, ANDA#74-586. Reference is made to our ANDA submissions dated December 8, 1994, December 19, 1995, the agency's letter dated July 16, 1996, and Alpharma's amendments dated October 22, 1996, and April 30, 1997. Reference is also made to telephone conversations on May 19, 1997 between Mr. Joseph Buccine and Dr. Nished of the agency, and Vincent Andolina of Alpharma. In these telephone conversations the agency requested that we revise our specifications for impurities and add a commitment to include a dissolution specification for the suppositories.

The agency's comments are being restated and our response follows:

1. **All known impurity limits for the drug substance should be set at — rather than the — submitted. For the dosage forms, release and stability specifications of — per individual impurity/degradant would be acceptable. Total impurity limit of — for the drug substance and dosage forms would be acceptable.**

Alpharma commits to revise our drug substance and dosage form specifications in accordance with the agency's request as follows:

A. Miconazole Nitrate USP Drug Substance: The tests for ——— and other individual impurities will reflect a release specification of Not More Than ———

B. Miconazole Nitrate Vaginal Cream USP 2%: The tests for ——— and other individual impurities will reflect release and stability specifications of Not More Than ———

MAY 23 1997

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

C. Miconazole Nitrate Vaginal Suppositories USP 100 mg: The tests for [redacted] and other individual impurities will reflect release and stability specifications of Not More Than [redacted]

2. Submit commitment for dissolution test specification for suppositories post approval.

Please note that Alpharma submitted in the Amendment dated April 30, 1997 (Pages 239 and 253) the following dissolution test specification for release and stability: NLT [redacted] (Q) in 3 hours.

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to FDA's Atlanta district office.

Sincerely,
Alpharma

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB:dc

cc: New York District Office
Atlanta District Office

ALPHARMA U.S. Pharmaceuticals Division

Facsimile Transmission

TO: Mr. Joseph Buccine
FDA, OGD, Div. Chemistry I

FAX NUMBER: (301) 594-0180
NO. OF PAGES: 6
(including cover)

FROM: Ron Bynum RB

DATE: May 21, 1997

SUBJECT: **M-Zole 7 Dual Pack**
Telephone Facsimile Amendment to ANDA #74-586

As you requested in your 5/19/97 telephone conversation with Vincent Andolina, attached please find a copy of subject (mailed today by overnight express).

APPEARS THIS WAY
ON ORIGINAL

Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 • Fax: (410) 558-7262

ALPHARMA
U.S. Pharmaceuticals Division

May 21, 1997

Office of Generic Drugs
CDER, FDA
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, Alpharma herewith submits an amendment for M-Zole 7 Dual Pack, ANDA#74-586. Reference is made to our ANDA submissions dated December 8, 1994, December 19, 1995, the agency's letter dated July 16, 1996, and Alpharma's amendments dated October 22, 1996, and April 30, 1997. Reference is also made to telephone conversations on May 19, 1997 between Mr. Joseph Buccine and Dr. Nished of the agency, and Vincent Andolina of Alpharma. In these telephone conversations the agency requested that we revise our specifications for impurities and add a commitment to include a dissolution specification for the suppositories.

The agency's comments are being restated and our response follows:

1. **All known impurity limits for the drug substance should be set at —— rather than the —— submitted. For the dosage forms, release and stability specifications of —— per individual impurity/degradant would be acceptable. Total impurity limit of —— for the drug substance and dosage forms would be acceptable.**

Alpharma commits to revise our drug substance and dosage form specifications in accordance with the agency's request as follows:

A. Miconazole Nitrate USP Drug Substance: The tests for ———— and other individual impurities will reflect a release specification of Not More Than ——

B. Miconazole Nitrate Vaginal Cream USP 2%: The tests for ———— and other individual impurities will reflect release and stability specifications of Not More Than ——

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

C. Miconazole Nitrate Vaginal Suppositories USP 100 mg: The tests for ——— ———————————, and other individual impurities will reflect release and stability specifications of Not More Than ——

2. **Submit commitment for dissolution test specification for suppositories post approval.**

Please note that Alpharma submitted in the Amendment dated April 30, 1997 (Pages 239 and 253) the following dissolution test specification for release and stability: NLT ——— (Q) in 3 hours.

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to FDA's Atlanta district office.

Sincerely,
Alpharma

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB:dc

cc: New York District Office
Atlanta District Office

M-Zole 7 Dual Pack
Amendment to ANDA#74-586
Alpharma USPD Inc.

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

May 21, 1997 TELEPHONE FACSIMILE AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), Alpharma, U.S. Pharmaceuticals Division certifies that the field copy is a true copy of the technical sections of this amendment, and the field copy has been sent to the Atlanta district office.

Ronald Bynum 5/21/97

Ronald Bynum
Manager, Regulatory Affairs

Date

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314)

Form approved: OMB No. 0910-0001. Expiration Date: April 30, 1994. See OMB Statement on Page 3

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT	DATE OF SUBMISSION
Alpharma, U.S. Pharmaceuticals Division	May 21, 1997
ADDRESS *(Number, Street, City, State, and Zip Code)*	TELEPHONE NO. (Include Area Code)
333 Cassell Drive, Suite 3500 Baltimore, Maryland 21224	(410) 558-7250
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* ANDA #74-586

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
Miconazole Nitrate Vaginal Suppositories USP, 100 mg Miconazole Nitrate Cream USP, 2%	M-Zole 7 Dual Pack

CODE NAME (If any)	CHEMICAL NAME
N/A	1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]imidazole mononitrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Vaginal Suppositories/Vaginal Cream	Intravaginal/Topical for the Vulva	100 mg/2%

PROPOSED INDICATIONS FOR USE

For the treatment of vaginal yeast infections and the relief of external vulvar itching and irritation associated with a yeast infection.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Monistat® 7 Combination Pack	ADV Care

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☒ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

This application contains the following items: (Check all that apply)

	1. Index
	2. Summary (21 CFR 314.50(c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Telephone Facsimile Amendment to a Pending Application.

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ronald Bynum, Manager, Regulatory Affairs	Ronald Bynum	5/21/97

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
333 Cassell Drive, Suite 3500, Baltimore, Maryland 21224	(410) 558-7250

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

ALPHARMA
U.S. Pharmaceuticals Division

April 30, 1997

ORIG AMENDMENT
N/AM

Office of Generic Drugs
CDER, FDA
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, Alpharma, U.S. Pharmaceuticals Division (formerly NMC Laboratories and Barre-National) herewith submits an amendment for M-Zole 7 Dual Pack, ANDA#74-586. Reference is made to our ANDA submissions dated December 8, 1994, December 19, 1995, the Agency's letter dated July 16, 1996, Alpharma's 10/22/96 amendment, and the letter dated 1/10/97 to FDA's New Jersey district office from [redacted] formerly owned by Alpharma, now a subsidiary of [redacted] (enclosed).

Also, we make reference to the March 16, 1995 meeting between members of the parent company ALPHARMA$_{TM}$ (formerly A.L. Pharma, Inc.) and FDA's Office of Generic Drugs (Dr. F. Holcombe, R. Patel, et al) regarding Alpharma's plans to transfer the manufacturing site of 26 drug products previously submitted to the agency as ANDAs. Reference is also made to the March 17, 1995 site transfer meeting between Alpharma -Lincolnton and FDA's Atlanta District (Mr. B. Graham, P. Campbell, et al) concerning these changes, and FDA's 9/26/95 letter from Dr. Ganley regarding NMC's [redacted] Reference Number OGD 95-162, attached in section II.E). This submission consists of three volumes. Volumes 1 and 2 contain the amendment, and volume 3 contains two additional copies of the method validation reports.

RECEIVED
MAY 0 1 1997
GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

Upon submission of the original ANDA dated December 8, 1994, Alpharma had intended to use Miconazole Nitrate Cream USP, 2.0% manufactured at Alpharma-NMC's facility in Glendale, NY, and Miconazole Nitrate Vaginal Suppositories USP, 100 mg manufactured at

[redacted]

With this amendment we are seeking approval to manufacture both the Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg at our manufacturing facility in Lincolnton, NC:

Alpharma, U.S. Pharmaceutical Division
1877 Kawai Road
Lincolnton, North Carolina 28092

And, to withdraw from the application:

NMC Laboratories Inc. and [redacted]
70-36 83rd Street
Glendale, New York 11385

as manufacturers of the M-Zole 7 Dual Pack (the drug product).

Section I entitled, "Summary of Proposed Changes" describes the changes proposed in this amendment which will allow Alpharma to manufacture the M-Zole 7 Dual Pack drug product at our Lincolnton facility. We have enclosed twelve copies of the final printed labeling for the tube, carton, foil, and insert in section VI of this amendment.

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to FDA's Atlanta, GA district office.

Sincerely,
Alpharma

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs
cc: Atlanta District Office

ALPHARMA
U.S. Pharmaceuticals Division

M-Zole 7 Dual Pack
Amendment to ANDA#74-586
Alpharma USPD Inc.

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of the amendment dated April 30, 1997 and has been sent to the Atlanta District FDA Office.

Ronald Bynum
Ronald Bynum
Manager, Regulatory Affairs

4/30/97
Date

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

April 30, 1997

Mr. Ballard Graham
Director, Atlanta District Office
Food and Drug Administration, HFR-SE1
60 Eighth St. NE
Atlanta, GA 30309

Re: ANDA # 74-586
M-Zole 7 Dual Pack (Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg)

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Graham:

Enclosed is a copy of the amendment dated April 30, 1997 for [redacted]
Reference is made to the March 17, 1995 site transfer meeting between Alpharma - Lincolnton, NC/ ALPHARMA$_{TM}$ (formerly A.L. Pharma, Inc.) and members of your district office (Mr. P.Campbell et al) concerning the submission of these changes. We certify that this field copy is a true copy of the technical section contained in the archival and review copies of the amendment.

Sincerely,

Ronald Bynum
Manager, Regulatory Affairs

Enclosure

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

74-586

ALPHARMA
U.S. Pharmaceuticals Division

NEW CORRESP

February 7, 1997

WC NAF

ISI 2-27-97

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **Contact Persons for Abbreviated New Drug Applications and Abbreviated Antibiotic Drug Applications**

Dear Mr. Sporn,

Reference is made to the February 3, 1997 teleconference between Mr. Joe Buccine (OGD, FDA) and Mr. Ronald Bynum (Alpharma) concerning contact persons for abbreviated applications. A listing of Alpharma U.S.P.D's abbreviated applications and the respective contact persons is attached. Alpharma requests that FDA's queries pertaining to Alpharma's applications be addressed to either Mr. Vincent Andolina, Senior Manager, Regulatory Affairs at (410) 558-7250, extension 209 or Mr. Ronald Bynum, Senior Manager, Regulatory Affairs at (410) 558-7250, extension 208, as indicated on the attached listing. Both individuals have offices located at the following address:

Alpharma, U.S.P.D.
Johns Hopkins Bayview Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Telefax: (410) 558-7258.
Alternate telefax: (410) 558-7262.

Sincerely,

Stanley A. Kaplan, Ph.D.
Senior Vice President
Research and Development

enclosure
SK:rb

f:\...\nmc\products\380\submiss\andacntc.ltr

RECEIVED
FEB 14 1997
GENERIC DRUGS

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7262

ALPHARMA™
U.S. Pharmaceuticals Division

TPL

NDA 74-586 AMENDMENT

October 22, 1996

RECEIVED
OCT 23 1996
GENERIC DRUGS

Approval Summary
issued 11/20/96
/S/

Douglas Sporn, Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA #74-586
Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package)

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Sporn:

Pursuant to 21 CFR 314.96 (a) (1), Alpharma, U.S. Pharmaceuticals Division (formally known as NMC Laboratories Inc.) herewith submits an amendment to the abbreviated new drug application for the above mentioned drug product. Reference is made to the Administration's letter dated July 16, 1996 (attached) and to our ANDA submissions dated December 8, 1994 and December 19, 1995. The Administration's comments have been restated and Alpharma's responses follow.

A. Chemistry Deficiencies:

1. **Please revise your specifications for the drug substance to include limits and specifications for residual organic solvents, ——— ——— other individual impurities, and total impurities. The total should not be more than ← including the ordinary impurities. Please provide the results.**

A number of samples were utilized to test for residual organic solvents, ——— ——— , other individual impurities, and total impurities in the drug substance, Miconazole Nitrate, USP. Upon evaluation of the collected test results, the following specifications and limits are being proposed:

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7262

Redacted 3

pages of trade secret and/or confidential commercial information

1. Twelve Final Printed Suppository foil
2. One (1) tube cromalin and 11 copies
3. One (1) carton cromalin and 11 copies
4. Twelve Final Printed Inserts

See pages 31-34 of this amendment.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

A side-by-side comparison of the labeling submitted in the last submission (December 19, 1995) and this submission (October 22, 1996) is included in this amendment. The differences in the two submission have been annotated and explained. See pages 35-45 of this amendment.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

A. The firms referenced in your application regarding the manufacturing and testing should be in compliance with CGMP's at the time of approval of the application.

We acknowledge the agency's comments regarding CGMP compliance at the time of approval for the manufacturing and testing firms referenced in our application.

B. Your bio waiver request is under review.

On August 7, 1996, the Division of Bioequivalence issued a letter indicating that its review had been completed, and there are no questions at this time. See page 46 of this amendment.

C. USP methods are the regulatory methods and will prevail in the event of dispute.

We acknowledge the agency's comment that USP methods will prevail in the event of dispute.

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to FDA's Brooklyn, New York district office.

We trust that our response fully addresses the Administration's concerns.

Sincerely,
Alpharma

Ronald Bynum /for

Deborah Miran
Sr. Director, Regulatory Affairs
DM/ckj
enclosure

ALPHARMA™
U.S. Pharmaceuticals Division

October 22, 1996

Mr. Edward T. Warner, Director
New York District Office
Food and Drug Administration
850 3rd Avenue
Brooklyn, New York 11232-1593

RE: ANDA #74-586
Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package).

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Warner:

Pursuant to 21 CFR 314.96 (b), Alpharma, U.S. Pharmaceuticals Division hereby submits a field copy of our amendment dated October 22, 1996 to our pending abbreviated new drug application for Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package). The undersigned official certifies that the field copy is a true copy of the technical information contained in the amendment.

Sincerely,
Alpharma

Ronald Bynum /for

Deborah Miran
Sr. Director, Regulatory Affairs

DM/ckj

f:\...\nmc\products\730\submiss\071696dl.apa

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7262

Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package)
ANDA #74-586

October 22, 1996 MINOR AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96 (b), Alpharma, U.S. Pharmaceuticals Division certifies that the field copy is a true copy of the technical sections of this amendment, and the field copy has been sent to the Brooklyn FDA District Office.

Ronald Bynum/for
Deborah Miran
Sr. Director, Regulatory Affairs

10/23/96
Date

APPEARS THIS WAY
ON ORIGINAL

f:\...\nmc\products\730\submiss\071696dl.apa

ALPHARMA™
U.S. Pharmaceuticals Division

NEW CORRESP

August 30, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA #74-586

(Miconazole Nitrate Vaginal Suppositories, 100 mg
and Miconazole Nitrate Cream, 2 %)

TRANSFER OF OWNERSHIP OF AN PENDING APPLICATION

Dear Mr. Sporn:

On June 20, 1996 Alpharma, U.S. Pharmaceuticals Division acquired the ownership of, and all right, title and interest of any nature in the above-referenced abbreviated new drug application. In accordance with 21 CFR § 314.72(a)(2), we are notifying the Food and Drug Administration of transfer of ownership from NMC Laboratories, Inc., 333 Cassell Drive, Suite 3500, Baltimore, Maryland 21224. Barre/NMC have been wholly owned subsidiaries of Alpharma USPD. Accordingly, we are transferring ownership to the new company name.

Enclosed is a completed, signed Form FDA-356H specifying Alpharma, U.S. Pharmaceuticals Division as the applicant.

Sincerely,
ALPHARMA

Deborah Miran
Sr. Director, Regulatory Affairs

Enclosure

RECEIVED
SEP 0 3 1996
GENERIC DRUGS

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7258

FAXED 7/17/96 /S/

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DATE: July 17, 1996

TO: NHC Laboratories

Attn: Deborah Miraw

PHONE: (410) 558-7250

FAX: (410) 558-7258

NUMBER OF PAGES: 4
(Excluding Cover Sheet)

/S/ for

FROM: William Russell

PHONE: (301) 594-1841

FAX: (301) 594-0180

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: 74-586 DATE OF LETTER: July 16, 1996

NAME OF DRUG PRODUCT: Miconazole Nitrate Vaginal Suppositories, USP

SPECIAL INSTRUCTIONS:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-586

NMC Laboratories, Inc.
Attention: Deborah Miran
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

JUL 16 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 8, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package).

Reference is also made to your amendment dated December 19, 1995.

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

A. Chemistry Deficiencies:

[redacted]

[

]

B. Labeling Deficiencies

1. GENERAL COMMENT

We have forwarded your proposed proprietary name of _____ to the CDER Labeling and Nomenclature Committee for review and comment. We defer final comment on your labels and labeling pending resolution of this issue. We will notify you of their comments, when received.

2. CONTAINER

a. Suppositories - Satisfactory in draft but see GENERAL COMMENT.

b. External Vulvar Cream (9 g) (Front Panel)

i. Enhance the prominence of the product's proprietary name, "MICONAZOLE NITRATE EXTERNAL VULVAR CREAM".

ii. Revise the storage recommendations to read, "Store at controlled room temperature..."

3. CARTON

a. See GENERAL COMMENT.

b. Tag Front and Front Panel

Revise to delete _____ appearing on the left side. The wording is redundant.

c. Tag Back (WARNINGS)

Revise the third bullet to delete the following "BAD" _____

d.

[

]

e. See comment (b)(ii) under CONTAINER.

4. INSERT (EDUCATIONAL BROCHURE)

a. Revise to delete ' [redacted]" from the statement of identity to be consistent with the listed drug.

b. Revise the following statement and place it immediately below the statement of identity:

"CURES MOST VAGINAL YEAST INFECTIONS AND RELIEVES ASSOCIATED ITCHING AND IRRITATION"

c. SYMPTOMS OF VAGINAL YEAST INFECTIONS

Revise symptom #2 to read, "A clumpy, vaginal..." (delete [redacted])

d. WARNINGS

Please ensure that this section is boxed and shaded.

e. DIRECTIONS FOR USE

Revise sentence 2 of Direction #1 to read,

Tear the foil at the "V". Cut and peel... (make 2 sentences)

f. See comment (b)(ii) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in draft. Do not submit final printed labeling until you are notified that a decision regarding your proposed proprietary name has been reached by the CDER Labeling and Nomenclature Committee.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

A. The firms referenced in your application regarding the manufacturing and testing should be in compliance with CGMP's at the time of approval of the application.

B. Your bio waiver request is under review.

C. USP methods are the regulatory methods and will prevail in the event of dispute.

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. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalance 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

APPEARS THIS WAY
ON ORIGINAL

2.1
A. Weikel

ANDA 74-586

MAY - 6 1996

NMC Laboratories, Inc.
Attention: Deborah Miran
333 Cassell Drive
Suite 3500
Baltimore MD 21224

Dear Madam:

Reference is made to the request for waiver of *in vivo* bioequivalence, submitted on December 8, 1995 and was acceptable for filing on December 20, 1995, for Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package).

The Office of Generic Drugs has reviewed the bioequivalence data submitted for this application and has found the data submitted to be incomplete. The following comments are provided for your consideration:

1. The *in vivo* bioequivalence data required for approval is dependent on the approval of two separate applications [Miconazole Nitrate Vaginal Suppositories, USP 100 mg (ANDA# 74-507) and Miconazole Nitrate Cream 2% (ANDA# 74-164)] both owned by NMC Laboratories.

2. Though ANDA 74-507 (suppositories) has been approved ANDA 74-164 (cream) is still under review by the Agency.

3. Until ANDA 74-164 is reviewed and deemed acceptable the Agency will defer review of the bioequivalence data for the combination pack application. You are advised to submit a request for this application to be reviewed once ANDA 74-164 (cream) is approved.

As described under 21 CFR 314.96 an action which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., Consumer Safety Officer at (301) 594-0315. 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

ANDA 74-586

NMC Laboratories, Inc.
Attention: Deborah Miran
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

FEB 2 1996

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.

Reference is also made to our "Refuse to File" letter dated February 3, 1995, and your amendment dated December 19, 1995.

NAME OF DRUG: Miconazole Nitrate Cream USP, 2%, and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package)

DATE OF APPLICATION: December 8, 1994

DATE OF RECEIPT: December 12, 1994

DATE ACCEPTABLE FOR FILING: December 20, 1995

Reference is also made to your correspondence dated January 2, 1996, and January 17, 1996.

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.

Should you have questions concerning this application, contact:

Anna Marie Weikel
Consumer Safety Officer
(301) 594-1841

Sincerely yours,

/S/ 2/2/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-586
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB /S/ 1/30/96 date
HFD-615/WRussell, CSO /S/ /S/ date
HFD-629/PSchwartz, Sup. Chem /S/ date 1/31/96
X:\new\firmsnz\nmc\ltrs&rev\74-586
F/T bcw/1-22-96
ANDA Acknowledgement Letter!

NMC LABORATORIES INC.

RECEIVED

NEW CORRESP BIOAVAILABILITY JUN 25 1996

NC 810

OKP

GENERIC DRUGS

June 13, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #74-586**
Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package)

Dear Mr. Sporn,

Pursuant to 21 CFR 314.96(a)(1), NMC Laboratories herewith submits an amendment to the above referenced pending application. Reference is made to the Administration's letter of May 6, 1996 (attached) and to our application of December 8, 1994 and our amendment of 12/19/95. The Administration's comments have been restated and NMC's response follows.

1. **The *in vivo* bioequivalence data required for approval is dependent on the approval of two separate applications [Miconazole Nitrate Vaginal Suppositories, USP 100 mg (ANDA# 74-507) and Miconazole Nitrate Cream 2% (ANDA# 74-164)] both owned by NMC Laboratories.**

2. **Though ANDA 74-507 (suppositories) has been approved ANDA 74-164 (cream) is still under review by the Agency.**

3. **Until ANDA 74-164 is reviewed and deemed acceptable the Agency will defer review of the bioequivalence data for the combination pack application. You are advised to submit a request for this application to be reviewed once ANDA 74-164 (cream) is approved.**

   ANDA 74-164 for Miconazole Nitrate Vaginal Cream, 2% was approved by the FDA on March 29, 1996 (page 2). Therefore, NMC requests that the bioequivalence data for this combination pack application be reviewed.

Sincerely,
NMC Laboratories Inc.

Deborah Miran
Sr. Director, Regulatory Affairs

DM:rb
enclosure

f:\...\729\submiss\050696dl.ama

70-36 83rd Street, Glendale, NY 11385 • (718) 326-1500
Fax Numbers 1-800-255-7588 (Outside New York State)
718-894-3218 (Within New York State)

NMC LABORATORIES INC.

January 17, 1996

NEW CORRESP

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Charles Ganley, MD, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA #74-586

CORRESPONDENCE

Dear Dr. Ganley:

Pursuant to 21 CFR 314.96(a)(1), MC herewith submits an amendment to the above referenced unapproved abbreviated application. Reference is made to the Administration's telephone call of January 2,1996. In this telephone call, we were requested to revise our third copy certification statement. The requested revisions have been made and accordingly, a revised, signed certification statement is attached.

Sincerely,

NMC Laboratories, Inc.

Deborah Miran
Sr. Director, Regulatory Affairs

Enclosure

DM/jb

RECEIVED
JAN 18 1996
GENERIC DRUG

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718-894-3218 (Within New York State)

NMC LABORATORIES INC.

ANDA #74-586

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), NMC certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA District Office.

Deborah Miran
Sr. Director, Regulatory Affairs

1-17-96
Date

APPEARS THIS WAY
ON ORIGINAL

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Fax Numbers 1-800-255-7588 (Outside New York State)
718-894-3218 (Within New York State)

NMC LABORATORIES INC.

January 2, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Charles Ganley, MD, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

wrong ANDA #
wrong drug product
Wrong ANDA date

Re: ANDA ~~#74-164~~ 74-586
Miconazole Nitrate Vaginal Cream, 2%

CORRESPONDENCE

Dear Dr. Ganley:

Pursuant to 21 CFR 314.96(a)(1), MC herewith submits an amendment to the above referenced unapproved abbreviated application. Reference is made to the Administration's telephone call of January 2, 1996 regarding our Abbreviated New Drug Application dated December 30, 1991. In this telephone call, we were requested to revise our third copy certification statement. The requested revisions have been made and accordingly, a revised, signed certification statement is attached.

Sincerely,

NMC Laboratories, Inc.

Deborah Miran
Sr. Director, Regulatory Affairs

Enclosure

DM/jb

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Fax Numbers 1-800-255-7588 (Outside New York State)
718-894-3218 (Within New York State)

NMC LABORATORIES INC.

Miconazole Nitrate Vaginal Cream, 2%
ANDA #74-164

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), NMC certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA District Office.

Deborah Miran
Sr. Director, Regulatory Affairs

1/2/96
Date

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

70-36 83rd Street, Glendale, NY 11385 • (718) 326-1500
Fax Numbers 1-800-255-7588 (Outside New York State)
718-894-3218 (Within New York State)

NMC LABORATORIES INC.

NDA ORIG AMENDMENT
N/AC

505(b)(2)(W) information acceptable for filing
/S/ 1/2/96
/S/ 11/26/96

December 19, 1995

RECEIVED
DEC 20 1995
GENERIC DRUGS

Review completed 6/19/96 /S/

Office of Generic Drugs
CDER,FDA
Attn: Charles Ganley, MD, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA #74-586
Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package)

Dear Dr. Ganley:

Pursuant to 21 CFR 314.96 (a)(1), NMC herewith submits an amendment to the above referenced ANDA. Reference is also made to the Administration's letter of February 3, 1995 (attached) and to our ANDA submission of December 8, 1994. The Administration's comments have been restated and NMC's responses follow.

Your exhibit batch records for your proposed suppository dosage form do not include the batch yield. In addition, your packaging records for this batch appear to indicate that the [redacted] The exhibit batch must be a dedicated batch to support approval of this specific ANDA.

The batch yield for the suppository dosage form exhibit batch (Lot #404003) is enclosed as page 002.

New dedicated exhibit batches for the suppository and cream have been produced to support approval of this ANDA. A copy of the complete batch record for both dosage forms are enclosed as pages 003-043 and 044-103, respectively.

Analytical results for both dosage forms are enclosed as pages 104-106 (suppository) and 107-130 (cream). Raw material test records for the materials used in the new exhibit batches are enclosed as pages 131-169 (suppository) and 170-227 (cream). Container/ closure testing records for the packaging components used in the new exhibit batches are enclosed as pages 228-241 (suppository) and 242-254 (cream). Stability summaries for the new exhibit batches are enclosed as pages 255-293 (suppository) and 294-340 (cream).

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718-894-3218 (Within New York State)

Although you have provided a *qualitative* comparison of the formulation for your proposed drug product with that of the reference listed drug product, you have not provided a comparison demonstrating that the proposed drug product is *quantitatively* the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your drug product and the reference listed drug product, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)].

This information to demonstrate safety should include, but is not limited to: (a) information that demonstrates that the inactive ingredients have been previously approved in a drug product administered by the same route of administration; (b) information that demonstrates that the concentration of the inactive ingredients is within the concentration range previously approved for drug products administered by the same route of administration; (c) a comparison of the physical and chemical properties (eg, pH, viscosity) of the proposed drug product with that of the reference listed drug; (d) information to show that any changes in inactive ingredients do not adversely affect these properties.

A quantitative comparison between the proposed drug products and the reference drug products is enclosed as page 341.

a) The suppository dosage form was approved on 11/19/93 (ANDA #73-507). This is proof that the proposed drug product suppository dosage form inactive ingredients have been previously approved in a drug product administered by the same route of administration.

In addition, the labeling side-by-side comparison (pages 362-375) illustrates that the inactive ingredients in the proposed drug products (cream and suppository) are the same as those in the reference drug products (cream and suppository). This is proof that the cream and suppository dosage form inactive ingredients have been previously approved in a drug product administered by the same route of administration.

b) The suppository dosage form was approved on 11/19/93 (ANDA #73-507). This is proof that the concentration of the proposed drug product suppository dosage form inactive ingredients is within the range previously approved in a drug product administered by the same route of administration.

In addition, the quantitative composition comparisons for the proposed drug products (cream and suppository) and the referenced listed drug products demonstrate that the concentration of inactive ingredients for both proposed drug products is within the range previously approved for drug products administered by the same route of administration (page 341).

c) Comparative chemical testing of the test and reference cream drug products were submitted in Section VI of the bio-study in the 5/21/93 amendment to ANDA #74-164 (pages 344-346 of this amendment). Additional comparative chemical and physical test data for the proposed drug products (cream and suppository) and the reference listed drug products are enclosed as pages 347-349.

d) The manufacturing instructions for the proposed drug products (cream and suppository) do not allow for changes in inactive ingredients (pages 377-388 and 389-413, respectively). Therefore, there is no concern about changes in inactive ingredients affecting physical and chemical properties.

Please be advised that *in vivo* bioequivalence studies with clinical endpoints are required for both products (cream and vaginal suppositories).

Based on the 9/26/95 Office of Generic Drugs correspondence Reference Number OGD 95-159, it was determined that the *in vivo* bioequivalence studies submitted in support of both single applications could be referenced for this combination drug product since NMC is the applicant for the relevant applications (pages 350-351). The *in vivo* bioequivalence study for the suppository dosage form was submitted in the 2/12/91 amendment to the application (ANDA #73-507). The *in vivo* bioequivalence study for the cream dosage form was submitted in the 5/21/93 amendment to the application (ANDA #74-164).

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Based upon this amendment, the submission should be filed as an abbreviated new drug application.

In addition, you have listed [redacted] and [redacted] for the active ingredient. Please be aware that batch records and stability data from exhibit batches using these alternates sources must be submitted for approval prior to using these sources for the marketed proposed drug product. Information submitted in prior applications is not transferable to this application.

The [redacted] of the miconazole nitrate active ingredient are being withdrawn at this time. The [redacted] of the miconazole nitrate drug substance used in the new exhibit batches are as follows.

[redacted]

These [redacted] are being submitted for approval.

Also, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of the draft labeling in the archival copy of the application. You provided two copies. Please provide two additional copies of the draft labels and labeling for the archival copy. In the future please include *four* copies of the draft labels and labeling in *both* the archival and review copies.

Changes have been made to the draft labels and labeling, so four copies of the revised draft labels and labeling are enclosed as pages 352-361.

Copy of Final Printed Suppository labeling (page 352).
Copy of Draft Cream tube labeling (page 353).
Copy of Draft Carton labeling (page 354-356).
Copy of Draft Insert labeling (pages 357-361).

Although you indicate that a third copy was sent to the FDA district office, you must include a certification with an original signature that this is a "true copy" of the technical sections. Refer to Sections 314.94(d)(5) and 314.444 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352. Please provide this certification.

The signed December 8, 1994 cover letter to the ANDA contained a statement certifying that a copy was sent to the FDA district office. The signed December 8, 1994 cover letter to the FDA district office contained a statement certifying that the copy was a true copy of the technical sections (page 376). NMC is continuing this practice and in order to make the certification even more thorough, NMC is now also including a separate certification statement to the application itself.

Since revised MPCRs (revised relative to the MPCRs previously submitted as pages 289-304 for the suppositories and 306-329 for the cream of the 12/8/94 application] were used to produce the new exhibit batches, blank copies of these revised MPCRs are enclosed as pages 377-388 (suppository) and 389-400 and 401-413 (cream). A brief description of the revisions made to the MPCRs is included. For the cream dosage form, revised [redacted] and [redacted] MPCRs will be submitted to this application at a later date. NMC intends to utilize batch sizes of [redacted] for the cream drug product.

We are taking this opportunity to make several corrections in the information previously provided in the 12/8/94 ANDA submission.

Page 010, Proposed Labeling section: The first paragraph indicates the presence of a [redacted] cream label". The correct container size is 9 gm. The reference to ounces is in error.

Page 264, Name and Address of Outside Firms: the name of the [redacted] listed at the top of the page is missing. The [redacted] is:

[redacted]

Pursuant to 21 CFR 314.96 (b), NMC certifies that a field copy of this amendment to the application has been sent to the FDA district office.

Sincerely,
NMC LABORATORIES, INC.

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb
enclosure

APPEARS THIS WAY
ON ORIGINAL

f:\..\730\submiss\020395dl.ama

NMC LABORATORIES INC.

Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package)
ANDA #74-586

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96 (b), NMC certifies that a field copy of this amendment to the application has been sent to the FDA District Office.

Deborah Miran
Sr. Director, Regulatory Affairs

12/19/95
Date

APPEARS THIS WAY
ON ORIGINAL

f:\...\730\submiss\020395dl.ama

70-36 83rd Street, Glendale, NY 11385 • (718) 326-1500
Fax Numbers 1-800-255-7588 (Outside New York State)
718-894-3218 (Within New York State)

ANDA 74-586

NMC Laboratories, Inc.
Attention: Deborah Winkel
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

FEB 3 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated December 8, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg (combination package).

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:

Your exhibit batch records for your proposed suppository dosage form do not include the batch yield. In addition, your packaging records for this batch appear to indicate that the batch was packaged for specific customers. The exhibit batch must be a dedicated batch to support approval of this specific ANDA.

Although you have provided a **qualitative** comparison of the formulation for your proposed drug product with that of the reference listed drug product, you have not provided a comparison demonstrating that the proposed drug product is **quantitatively** the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your drug product and the reference listed drug product, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)].

This information to demonstrate safety should include, but is not limited to: (a) information that demonstrates that the inactive ingredients have been previously approved in a drug product administered by the same route of administration; (b) information that demonstrates that the concentration of the inactive ingredients is within the concentration range previously approved for drug products

administered by the same route of administration; (c) a comparison of the physical and chemical properties (eg, pH, viscosity) of the proposed drug product with that of the reference listed drug; (d) information to show that any changes in inactive ingredients do not adversely affect these properties.

Please be advised that *in vivo* bioequivalence studies with clinical endpoints are required for both products (cream and vaginal suppositories). Please contact Jason Gross, Consumer Safety Officer, Division of Bioequivalence at (301) 594-2290, for information regarding requirements for this specific combination product.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, you have listed alternate manufacturers and suppliers for the active ingredient. Please be aware that batch records and stability data from exhibit batches using these alternate sources must be submitted for approval prior to using these sources for the marketed proposed drug product. Information submitted in prior applications is not transferable to this application.

Also, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of the draft labeling in the archival copy of the application. You provided two copies. Please provide two additional copies of the draft labels and labeling for the archival copy. In the future please include **four** copies of the draft labels and labeling in **both** the achival and review copies.

Although you indicate that a third copy was sent to the FDA district office, you must include a certification with an original signature that this is a "true copy" of the technical sections. Refer to Sections 314.94(d)(5) and 314.444 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352. Please provide this certification.

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 conclusion, 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
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 2/3/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-586
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting /S/ 1/9/95 date
HFD-615/WRussell, CSO /S/ 1/9/95 date
HFD-610/JPhillips, Chief, LRB /S/ date
HFD-625/~~Smela~~ /S/ 2/1/95 4/10/95
WP File\russell\74\74-586
F/T bcw/1-6-95
ANDA Refuse to File!

ALPHARMA
U.S. Pharmaceuticals Division

August 27, 1998

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **M-Zole 7 Dual Pack**
(Miconazole Nitrate Cream USP, 2% and Miconazole Nitrate Vaginal Suppositories USP, 100 mg; Combination Package)
ANDA # 74-586

Dear Mr. Sporn:

Pursuant to 21 CFR §314.81(b)(2), Alpharma, U.S. Pharmaceuticals Division hereby submits the Annual Report for the referenced Abbreviated New Drug Application covering the reporting period of July 18, 1997 through July 17, 1998. The Annual Report submission consists of one volume.

Sincerely,

Vincent Andolina

Vincent Andolina
Manager, Regulatory Affairs

VA:ckj
Enclosures

K:\759\REGFILES\PRODUCTS\0729\SUBMISS\07970798.ANR

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258