

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number** 73249

**Trade Name** Gynix Vaginal Tablets 100mg

**Generic Name** Clotrimazole Vaginal Tablets USP 100mg

-  
**Sponsor** Copley Pharmaceutical, Inc.

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION 73249**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number     73249**

**APPROVAL LETTER**

FEB 13 1998

Copley Pharmaceutical, Inc.  
Attention: I. Nudelman  
25 John Road  
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated April 13, 1989, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Gynix Vaginal Tablets (Clotrimazole Vaginal Tablets, USP) 100 mg.

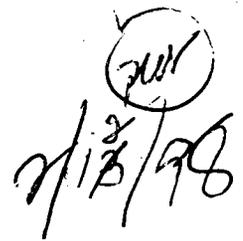
Reference is also made to your amendments dated April 27, 1993; May 17 and June 25, 1996; December 1, 17 and 24, 1997; and January 13, 1998.

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 Clotrimazole Vaginal Tablets USP, 100 mg to be bioequivalent to the listed drug (Gyne-Lotrimin® Vaginal Tablets, 100 mg, of Schering Plough Healthcare Products, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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,

  
\_\_\_\_\_  
Roger L. Williams, M.D.  
Deputy Center Director for  
Pharmaceutical Science  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      73249**

**FINAL PRINTED LABELING**

Cures most vaginal yeast infections  
**GYNIX**  
Clotrimazole vaginal tablets, USP

Cures most vaginal yeast infections

**GYNIX**  
CLOTRIMAZOLE VAGINAL TABLETS, USP  
100 mg  
ANTIFUNGAL

Full Prescription Strength  
Educational Pamphlet Enclosed.

7 Vaginal Tablets & Applicator (7-Day therapy)

**DO NOT TAKE BY MOUTH**

Cures most vaginal yeast infections  
**GYNIX**  
Clotrimazole vaginal tablets, USP

Cures most vaginal yeast infections

**GYNIX**  
Clotrimazole vaginal tablets, USP

Both ends of this package are sealed. Do not purchase if ends are open or show evidence of tampering.

**Active Ingredient:** Each tablet contains 100 mg clotrimazole

**Inactive Ingredients:** Corn starch, lactose, magnesium stearate, povidone, sodium lauryl sulfate.

RM 5840-1

# GYNIX

Clootrimazole Vaginal Tablets, USP

100 mg

## Cures most vaginal yeast infections

GYNIX Antifungal Vaginal Tablets can kill the yeast that may cause vaginal infection. They do not stain clothes.

**Indications:** For the treatment of vaginal yeast (Candida) infection.

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

**WARNING: DO NOT USE IF YOU HAVE ABDOMINAL PAIN, FEVER, OR FOUL-SMELLING DISCHARGE. CONTACT YOUR DOCTOR IMMEDIATELY.**

Before using, read the enclosed pamphlet.

**Directions:** Unwrap one tablet, place it in the applicator, and use the applicator to place the tablet into the vagina, preferably at bedtime. Repeat this procedure daily for 7 consecutive days.



8 38245-171-37 N

Clootrimazole vaginal tablets, USP

# GYNIX

Cures most vaginal yeast infections

**WARNING: 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 PROPERLY WITH PROPER TREATMENT, CONSULT YOUR DOCTOR. YOU COULD BE PREPARING FOR YOUR INFECTIONS UNDERLYING MEDICAL CAUSES OR YOUR INFECTIONS INCLUDING DIABETES OR A DAMAGED IMMUNE SYSTEM (INCLUDING DAMAGE FROM INFECTION WITH HIV - THE VIRUS THAT CAUSES AIDS). (PLEASE READ PATIENT PACKAGE LEAFLET FOUND INSIDE PACKAGE.)**

Do not use during pregnancy except under the advice and supervision of a doctor. Do not use tampons while using this medication. 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. **NOT FOR USE IN CHILDREN LESS THAN 12 YEARS OF AGE.**

If you have any questions about GYNIX or vaginal yeast infection, contact your physician.

Store at room temperature between 20° and 30°C (36° and 86°F).

See end panel of carton and foil wrappers for lot number and expiration date.

 Copley Pharmaceutical, Inc.  
Canton, MA 02021



READ THIS BEFORE USING

# GYNIX

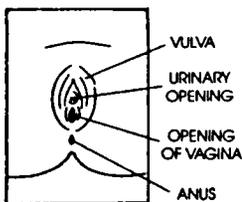
Clotrimazole Vaginal Tablets, USP  
100 mg

ANTIFUNGAL

FOR THE TREATMENT OF VAGINAL YEAST  
(CANDIDA) INFECTION

## 1 HOW TO RECOGNIZE A YEAST INFECTION.

GYNIX will cure most vaginal yeast (Candida) infections. But not every vaginal infection is caused by yeast. If this is the first time you are experiencing vaginal itch and discomfort, it is important to visit your doctor to be sure that yeast is the problem. Do not use if you have abdominal pain, fever, or foul-smelling discharge. You may have a condition more serious than a yeast infection, and you should see your doctor immediately.



The main symptom of yeast infection is itching which can be moderate to intense. The itching is usually in the folds of the vagina and on the skin outside (vulva).

Yeast infection may also cause a white discharge from the vagina. The discharge may be thick like paste or lumpy like cottage cheese. Underneath the discharge, the irritated skin of the vulva may be swollen and red, or may

have small red sore spots. The vagina may also feel sore inside or have a burning sensation, particularly during intercourse.

If you have one or more of these symptoms, especially in the days before your period, you could have a vaginal yeast infection.

## 2 GYNIX CAN KILL THE YEAST THAT CAUSES THE INFECTION.

To cure vaginal yeast infection, it is necessary to eliminate the yeast cells. GYNIX does more than just relieve itching. It can kill the yeast that cause vaginal infections.

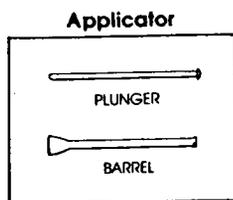
## 3 HOW TO USE

To treat vaginal yeast infections and relieve the associated symptoms of itching, burning, and discharge.

**WARNING: Do not take by mouth; for vaginal use only.**

### Directions:

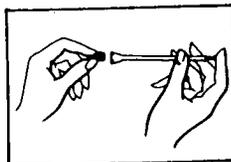
Using the applicator, place one tablet into the vagina, preferably at bedtime. Repeat this procedure for seven consecutive days.



**Important:** In order to kill the yeast completely, you must use GYNIX the full seven days, even if your symptoms are relieved sooner.

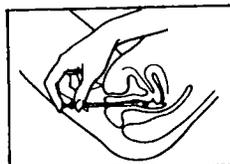
The plastic applicator provided with this package is specifically designed to permit proper placement of the vaginal tablets.

### To load the applicator:



Remove the vaginal tablet from its protective foil wrapping. Pull out the plunger of the applicator until it stops. Place the vaginal tablet into the end of the applicator barrel.

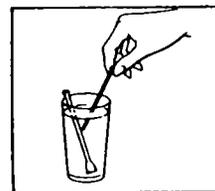
### To insert the vaginal tablet:



Lie on your back with knees bent. Grasp the barrel of the applicator with the thumb and middle finger. Place the insert end of the applicator into the vagina as deeply as it will go comfortably. Holding the applicator in place, press the plunger until it stops, depositing the tablet in the vagina. Withdraw the applicator.

### Care of the applicator:

After use, pull the plunger all the way out of the barrel. Wash both parts of the applicator in warm (not boiling), soapy water. Rinse thoroughly and dry. To reassemble, gently push the plunger back into the barrel as far as it will go.



**IMPORTANT:** Insert one GYNIX tablet each day for the full 7 days.

GYNIX usually starts to relieve itching and other symptoms within 3 days. 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. Discontinue use of the product and consult your doctor. Also, if symptoms recur within a 2-month period, contact your doctor.

**During your period, continue to use GYNIX. Its action is not affected by menstruation. However, do not use tampons while the medicine is in use; sanitary napkins may be used instead.**

GYNIX may reduce the effectiveness of some methods of birth control. Condoms, diaphragms, or vaginal spermicides may be so affected.

## 4 ARE THERE REASONS YOU GET YEAST INFECTIONS?

The vagina normally has a mixture of two kinds of germs called bacteria and yeast. Under certain conditions, the yeast in the vagina can grow too much — causing vaginal itching and, often, a discharge. In some women, the conditions that allow the yeast to multiply can include the use of birth control pills, routine hormonal changes, or taking antibiotics. Pregnancy and diabetes are two other important conditions that can lead to vaginal yeast infections. In women with frequently recurrent vaginal yeast infections, especially infections that don't clear up easily with proper treatment, the vaginal yeast infections may also be the result of serious medical conditions, including infection with HIV (the virus that causes AIDS), that can damage the body's normal defenses against infection.

### Hormonal changes are sometimes the cause.

Hormonal changes can cause some women to be prone to yeast infections. Some women get vaginal yeast infections during pregnancy, while taking birth control pills, or every month just before their period.

### Antibiotics are sometimes the cause.

Killing the normal bacteria of the vagina may allow yeast to multiply. That is why women taking antibiotics are more likely to get vaginal yeast infections.

### Damage to the body's normal defenses against infection is sometimes the cause.

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 VAGINAL YEAST INFECTIONS FREQUENTLY (THEY RECUR WITHIN A TWO MONTH PERIOD) OR IF YOU HAVE VAGINAL 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.**

**Can yeast be transmitted sexually?** Men usually do not get or spread yeast infections through sexual intercourse. However, if the woman's infection keeps recurring, she should ask her doctor about treating her partner, too.

**Cotton underpants may help.** Yeast flourish in a warm, moist environment. That is probably why yeast infections seem more common in the summertime. Since tight synthetic underpants and pantyhose can increase heat and moisture in the area of the vulva, cotton underpants are probably a better idea if you are prone to vaginal yeast infections.

### WARNINGS:

- Do not use if you have abdominal pain, fever, or a foul-smelling vaginal discharge. You may have a condition which is more serious than a yeast infection. Contact your doctor immediately.
- Do not use if this is your first experience with vaginal itch and discomfort. See your doctor.
- If there is no improvement within 3 days, you may have a condition other than a yeast infection. Stop using this product and see 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.
- If symptoms recur within a 2-month period, contact your doctor.
- Do not use during pregnancy except under the advice and supervision of a doctor.
- This medication is for vaginal use only. It is not to be taken by mouth. In case accidentally swallowed, seek professional assistance or contact a Poison Control Center immediately.
- Keep this and all drugs out of reach of children. This product is not to be used on children less than 12 years of age.

**If you have questions about GYNIX or vaginal yeast infections, contact your physician.**

**Active Ingredient:** Each tablet contains 100 mg clotrimazole

**Inactive Ingredients:** Corn starch, lactose, magnesium stearate, povidone, sodium lauryl sulfate

See bottom of carton and foil wrappers for lot number and expiration date.

**Store at room temperature between 2° and 30°C (36° and 86°F).**

Copley Pharmaceutical, Inc.  
Canton, MA 02021

Rev. 11/92  
RM #5839  
MG #8489

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      73249**

**CHEMISTRY REVIEW(S)**

# OFFICE OF GENERIC DRUGS

## ABBREVIATED NEW DRUG APPLICATION CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

**1. CHEMIST'S REVIEW NUMBER**

8 (EIGHT)

**2. ANDA NUMBER**

73-249

**3. NAME AND ADDRESS OF APPLICANT**

Copley Pharmaceutical, Inc.  
Attention: William E. Brochu  
25 John Road  
Canton, MA 02021

**4. LEGAL BASIS for ANDA SUBMISSION**

The reference drug product is Gyne-Lotrimin, Tablet 100 mg (Schering, Inc.).

**5. SUPPLEMENT(s)**

None

**6. NAME OF DRUG**

GYNIX (Clotrimazole Vaginal Insert, 100 mg)

**7. NONPROPRIETARY NAME**

Clotrimazole Vaginal Tablets

**8. SUPPLEMENT(s) PROVIDE(s) FOR**

None

**9. AMENDMENTS AND OTHER DATES**

4/13/1989	Date of submission of ANDA
4/27/1993	Submission of clinical bioequivalence study and response to Agency's deficiency letter of 1/15/1993.
9/1/1993	Submission of amendment.
12/9/1993	Response to deficiency letter of 10/27/1993
2/18/1994	Response to deficiency letter of 2/2/1994.
2/8/1996	Response to deficiency letter of 12/20/1995.
6/25/1996	Response to deficiency letter of 4/24/1995.
12/1/1997	Telephone amendment to response the T-Con on 11/10 and 11/18/97
12/17/97	Telephone amendment
1/13/97	Telephone amendment

**10. PHARMACOLOGICAL CATEGORY**

Antifungal

**11. HOW DISPENSED**

Over-the-counter (OTC)

**12. RELATED DMF(s)****13. DOSAGE FORM**

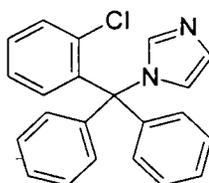
Tablets

**14. POTENCY**

100 mg

**15. CHEMICAL NAME AND STRUCTURE**

Clotrimazole. 1*H*-Imidazole, 1-[(2-chlorophenyl)diphenylmethyl]-.  $C_{22}H_{17}ClN_2$ . 344.85.  
23593-75-1

**16. RECORDS AND REPORTS**

None

**17. COMMENTS**

None

**18. CONCLUSIONS AND RECOMMENDATIONS**

The application is approvable.

**19. REVIEWER AND DATE COMPLETED**

Naiqi Ya, Ph.D./February 2, 1998

**OFFICE OF GENERIC DRUGS**  
**Review of Amendment to**  
**ABBREVIATED NEW DRUG APPLICATION**

**ANDA:** 73-249

**CHEMIST'S REVIEW NO.** 7 (seven)

**NAME AND ADDRESS OF APPLICANT:**

Copley Pharmaceutical, Inc.  
Attention: Jerome P. Skelly  
25 John Road  
Canton, MA 02021

**PURPOSE OF AMENDMENT:**

To respond to the Agency's deficiency letter of Dec. 20, 1995.

**DATE(S) OF SUBMISSION(S):**

April 13, 1989 - Date of submission of ANDA  
April 27, 1993 - Submission of clinical bioequivalence study and response to Agency's deficiency letter of 1-15-93.  
September 1, 1993 - Submission of amendment.  
December 9, 1993 - Response to deficiency letter of October 27, 1993  
February 2, 1994 - Deficiency letter.  
February 18, 1994 - Response to deficiency letter of 2-2-94.  
December 20, 1995 - Deficiency letter.  
February 8, 1996 - Response to def. letter of 12-20-95.

**PHARMACOLOGICAL CATEGORY:**

Antifungal.

**TRADE NAME:**

GYNIX (Clotrimazole Vaginal Insert, 100 mg)

**NONPROPRIETARY NAME:**

Clotrimazole Vaginal Tablets, 100 mg.

**DOSAGE FORM:**

Tablet

**POTENCY:**

100 mg.

**RX OR OTC:**

OTC, Possibly Rx

**SAMPLES:**

Not required.

RELATED IND/NDA/DMF:

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STERILIZATION:

Non-sterile drug product.

LABELING:

All container, carton and labeling issues were found previously to be satisfactory (C. Hoppes, 12-21-93). However, another issue of this product being marketed in both the OTC and Rx configuration has arisen over the past two plus years since labeling approval. See Tel-Con memo of C. Hoppes to B. Brochu of Copley (dated 1-17-96) in which labeling may have to be revised to encompass both marketed configurations. Current bioequivalence data supports only an OTC configuration, but does not support a Rx configuration. See additional comments under Bioequivalence Section of this review.

BIOEQUIVALENCY STATUS:

Clinical bioequivalence study has been submitted by applicant and is currently under review by Division of Anti-infective Drug Products (HFD-520) - as of May 4, 1993. Consultive review by HFD-520 has been completed (12-20-95) as well as review by OGD's Bioequivalence Division (J. Henderson, 2-8-96). The consultive review (dated 12-20-95) has been reviewed by OGD's Bioequivalence Division. The Agency analysis of the submitted data demonstrates that the submitted data has failed to establish the bioequivalence of Copley's test product to that of the reference listed drug. Copley has been notified of this analysis in OGD's letter dated 2-8-96 and has been considered to require a MAJOR amendment.

*The Agency has recently informed you in its letter dated 2-8-96 that your bioequivalence study fails to establish the bioequivalence of your drug product to that of the listed drug product.*

ESTABLISHMENT INSPECTION:

Updated EER's have been requested (10-30-95 and 11-8-95).  
No response to date. An additional request has been re-  
issued (3-12-96).

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS:

**PACKAGING:**

There is also an outstanding labeling/bioequivalence issue regarding Copley's desire to market this product in two configurations, i.e. an OTC version (100 mg daily, 7 times) and a  $\bar{R}$  version (100 mg BID, 3 times). Copley would prefer two marketed version, however, only one clinical trial (OTC version) clinical study has been received for review.

**STABILITY:**

Not applicable. Acceptable in previous review.

**REMARKS AND CONCLUSION:**

NA - Major because of major deficiencies cited in BIO review.

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the order of receipt:

Yes \_\_\_\_\_ No XXX \_\_\_\_\_

If no, explain reason(s) below:

Priority review given due to Minor amendment status.

RECALLS:

None

Reviewer:

A.J. Mueller

Date Completed:

March 13, 1996

cc: ANDA #73-249  
ANDA #73-249/Division File  
Field Copy

Endorsements:

HFD-627/A.Mueller/3-13-96 4-15-96

HFD-627/P.Schwartz, Ph.D./3-19-96 4/2/96

X:\NEW\FIRMSAM\COPLEY\LTRS&REV\73249N00.D07  
F/T MM April 2, 1996  
Not Approvable - Major

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      73249**

**ADMINISTRATIVE DOCUMENTS**

## ANDA APPROVAL SUMMARY

<b>ANDA:</b> 73-249	<b>CHEMIST:</b> Naiqi Ya, Ph.D.	<b>DATE:</b> February 2, 1998
<b>DRUG PRODUCT:</b> Clotrimazole Vaginal Tablets (GYNIX)		
<b>FIRM:</b> Copley Pharmaceutical, Inc.		
<b>DOSAGE FORM:</b> Tablets	<b>STRENGTH:</b> 100 mg	
<b>cGMP:</b> EER was found acceptable for all the establishments on June 4, 1997.		
<b>BIO:</b> Reviewed by Nhan L. Tran and found satisfactory on December 10, 1997.		
<b>VALIDATION - (Description of dosage form same as firm's):</b> Not required because of a compendial drug.		
<b>STABILITY:</b> The containers in the stability studies are identical to those in the container section.		
<b>LABELING:</b> Container, carton, and insert labeling were approved by C. Hoppers on December 23, 1997.		
<b>STERILIZATION VALIDATION (If applicable):</b> Not applicable.		
<b>SIZE OF BIO BATCH (Firm's source of NDS ok?):</b> The bio batch (171Z04) size is _____		
<b>SIZE OF STABILITY BATCHES (If different from bio batch, were they Manufactured via the same process?):</b> Two same size batches, 171Z04 (bio) and 171Z05 (manufactured at the new site), were used for stability studies.		
<b>PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:</b> The proposed production batches is _____ The manufacturing processes is identical to the exhibit batches.		
<b>Signature of chemist:</b>  2/2/98	<b>Signature of supervisor:</b>  2/2/98	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER            73249

CORRESPONDENCE

ORIGINAL

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton Commerce Center  
Canton, Massachusetts 02021  
(617) 821-6111

Fax:  
Canton (617) 821-4068  
Boston (617) 268-4394  
N.J. (201) 894-1553

18 February 1994

**NDA ORIG AMENDMENT**

AM

ROGER L. WILLIAMS, M.D.  
DIRECTOR  
OFFICE OF GENERIC DRUGS, CDER, FDA  
DOCUMENT ROOM 150  
METRO PARK NORTH II  
7500 STANDISH PLACE  
ROCKVILLE, MD 20855-2773

RE: CLOTRIMAZOLE VAGINAL TABLETS USP, 100mg  
ANDA 73-249  
AMENDMENT TYPE = MINOR

Dear Dr. Williams:

Enclosed is Copley Pharmaceutical's response to the deficiency comments listed in your division's deficiency notice of 2 February 1994, regarding our pending application for Clotrimazole Vaginal Tablets USP, 100mg.

compliance with all current cGMP's is provided.

We hope that this satisfies the review requirements for our submission and allows for subsequent approval.

Sincerely yours,  
*Bernie Grubstein*  
Regulatory Affairs

**RECEIVED**

FEB 22 1994

**GENERIC DRUGS**

25 FEB 94  
Mulline

ANDA: 73-249

Copley Pharmaceutical, Inc.  
Attention: Bernie Grubstein  
25 John Road  
Canton Commerce Center  
Canton, MA 02021

FEB 2 1994

Dear Sir:

This is in reference to your abbreviated new drug application dated April 13, 1989, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Clotrimazole Vaginal Tablets USP, 100 mg.

Reference is also made to your amendment dated December 9, 1993.

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

Chemistry Deficiency

---

In addition to responding to this deficiency, please note and acknowledge the following in your response:

---

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 the deficiency 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 bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

*1/26/94*  
*J* Rashmikant M. Patel, Ph.D  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA #73-249  
ANANDA #73-249/DUP/Division file  
Field Copy  
HFD-600/Reading file

Endorsements:

HFD-629/A.Mueller/1-13-94 *1-25-94*

HFD-613/C.Hoppes/1-18-94 *1/24/94*

HFD-619/P.Schwartz, Ph.D./1-14-94 *1/25/94*

HFD-629/J.Dawson/CSO/1-14-94 *1-26-94*

X:\Wpfile\Majors\Mueller\73249NOO.L03

F/T by MM 1-25-94

Deficiency letter - Minor Amendment

*dy*

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton Commerce Center  
Canton, Massachusetts 02021  
(617) 821-6111

Fax:  
Canton (617) 821-4068  
Boston (617) 268-4394  
N.J. (201) 894-1553

9 DECEMBER 1993

Roger L. Williams, M.D.  
Director  
Office of Generic Drugs (HFD-600)  
CDER, FDA  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20857

*TPL*  
ANDA SUB AMENDMENT  
*AM*

RE: CLOTRIMAZOLE VAGINAL TABLETS USP, 100mg  
ANDA 73-249  
AMENDMENT TYPE = MINOR

Dear Dr. Williams:

Enclosed are Copley Pharmaceutical's responses to the deficiency items listed in your division's 27 October 1993 review of our ANDA application for Clotrimazole Vaginal Tablets USP, 100mg.

This have been classified as a MINOR AMENDMENT.

Twelve (12) final label and insert in accordance with the listed revisions ~~are~~ also being provided.

We hope that this will complete the review process for this application and allow for its subsequent approval.

Thank you for your consideration.

Sincerely yours,

*Bernie Grubstein*  
Regulatory Affairs

RECEIVED

DEC 10 1993

GENERIC DRUGS

*noted*  
12-13-93

*13*  
*12-13-93*  
*Falton*

orig

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton Commerce Center  
Canton, Massachusetts 01921  
(617) 821-6111

Fax:  
Canton (617) 821-4068  
Boston (617) 268-4394  
N.J. (201) 894-1553

8 FEBRUARY 1996

RECEIVED

FEB 09 1996

GENERIC DRUGS

DIRECTOR  
OFFICE OF GENERIC DRUGS  
CDER, FDA  
METRO PARK NORTH II  
7500 STANDISH PLACE  
ROOM 150  
ROCKVILLE, MD 20855-2773

RE: CLOTRIMAZOLE VAGINAL TABLETS USP, 100mg (GYNIX)  
ANDA 73-249  
AMENDMENT TYPE = MINOR

MINOR AMENDMENT  
Am

Dear Sir:

Enclosed is Copley Pharmaceutical's responses to the items listed in your deficiency notice of 20 December 1995, relating to our ANDA application for Clotrimazole (GYNIX) Vaginal Tablets USP, 100mg.

We believe that our responses should satisfy the concerns raised in the deficiency notice and subsequently allow for approval of this application.

Sincerely yours,  
*Jerome P. Skelly*  
Jerome P. Skelly, PhD.  
Vice President, Scientific Affairs

Skelly

ANDA 73-249

Copley Pharmaceutical, Inc.  
Attention: W.E. Brochu, Ph.D.  
25 John Road  
Canton Commerce Center  
Canton, MA 02021

DEC 20 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated April 13, 1989, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for GYNIX (Clotrimazole Vaginal Tablets USP, 100 mg).

Reference is also made to your amendments dated February 18, 1994; and October 26, 1995.

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

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

Please commit that the bulk drug substance and final drug product will comply with current US Pharmacopeial specifications and methods.

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 review of your amendment, issuance

of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

12/20/95

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

cc: ANDA 73-249  
ANDA 73-249/Dup/Division File  
HFD-600/Reading File  
Field Copy

Endorsements:

HFD-629/A.Mueller/10/30/95 *12-14-95*  
HFD-629/P.Schwartz/11/1/95 *12/10/95*  
HFD-617/A.M.Weikel/12/1/95  
HFD-610/J.Phillips/11/15/95 *12/18/95*  
HFD-610/C.Hoppes/ *12/14/95*  
x:\wpfile\mueller\73249n00.106  
F/t by MM 12-14-95  
NOT APPROVABLE MINOR AMENDMENT

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

6/25/96

ORIG AMENDMENT  
*AC*

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER (HFD600)  
Food and Drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville MD 20855-2773

RE: Clotrimazole Vaginal Tablets USP 100mg  
ANDA# 73-249  
Major Deficiency Response

RECEIVED  
JUL 02 1996  
GENERIC DRUGS

Dear Mr. Sporn:

Reference is made to our ANDA and to the Agency's letters of 2/8/96 and 4/24/96.

We have responded to the Agency's bioequivalence questions provided in the 2/8/96 letter in our submission of 5/17/96. This submission addresses the questions listed in the Agency's 4/24/96 letter. Included in this submission is comparative in-vitro dissolution data requested by the Agency as a basis for approval of both the 7-day OTC and 3-day Rx dosing regimens and corresponding OTC and Rx product labeling. We have provided both Rx and OTC labeling proposals in our application and will await the Agency's comments on these before preparing and submitting final printed labeling.

We have provided a copy of this submission to FDA's New England District Office.

Please direct any questions related to this submission to me.

Sincerely,



W.E. Brochu, Ph.D.  
Director, Regulatory Affairs  
617-575-7520

*Handwritten note:*  
7-10-96

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

6/25/96

Richard Penta  
New England District  
Food and Drug Administration  
1 Montvale Ave  
Stoneham MA 02180-3500

RE: Clotrimazole Vaginal Tablets USP 100mg  
ANDA# 73-249  
Major Deficiency Response

Dear Mr. Penta:

Enclosed is a copy of our responses to the Agency deficiency letter of 4/24/96.

Please call me directly if there are any questions related to this submission.

Sincerely,



W.E. Brochu, Ph.D.  
Director, Regulatory Affairs  
617-575-7520

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

December 1, 1997

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER (HFD600)  
Food and Drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville MD 20855-2773

ANDA ORIG AMENDMENT

AC

**Amendment  
(Response to telephone deficiencies dated  
November 10, 1997 and November 18, 1997)  
Clotrimazole Vaginal Tablets 100mg  
ANDA# 73-249**

Reference is made to our ANDA # 73-249 for Clotrimazole Vaginal Tablets 100mg, USP submitted April 17, 1989, to the telephone discussion of November 10, 1997 between J. Buccini of the Office of Generic Drugs and W. E. Brochu of Copley Pharmaceutical Inc., to Copley's submission of November 12, 1997, and to the telephone discussion of November 18, 1997 between J. Buccini and I. Nudelman of Copley Pharmaceutical Inc. Details of the discussions are described below:

During the November 10, 1997 telephone contact, Mr. Buccine conveyed two deficiency points in Copley's application. The Agency requires Copley to set dissolution specifications for the finished product and stability and to provide stability data for lots 171Z04 and 171Z05. These deficiencies have been addressed by Copley (See Response # 1 and Response # 2 attachments).

In the November 12, 1997 submission, Copley proposed that the dissolution specification be set tentatively since Copley has limited dissolution data based on two batches of the drug product. However, Mr. Buccine indicated during the November 18, 1997 telephone discussion that the Agency rejected Copley's request for the tentative dissolution specification. Copley was advised to provide dissolution data which are out of specification if the requested specification cannot be met. In addition, a supplement requesting changes in the specification is mandated if Copley will not be able to meet the specification in the future.

RECEIVED

DEC 02 1997

GENERIC DRUGS

**Amendment**  
**(Response to telephone deficiencies dated**  
**November 10, 1997 and November 18, 1997)**  
**Clotrimazole Vaginal Tablets 100mg**  
**ANDA# 73-249**

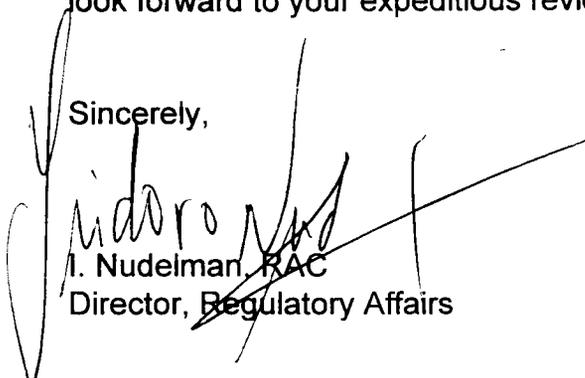
page 2

Based on the aforementioned telephone discussions, we have amended our finished product and stability specifications to include the requested dissolution specification as part of our ANDA commitment. Additionally we have provided a copy of an updated Stability Commitments and General Stability Protocol (Appendix 1).

We also acknowledge the fact that the Agency does not make recommendations for the USP to adopt a specification in a monograph for a drug product based on one ANDA only. It is understood that we may contact USP and propose the inclusion of the dissolution specification in the monograph for Clotrimazole Vaginal Tablets if so desired.

We believe the information included in this amendment adequately addresses all the deficiencies from the referenced telephone contacts. Please contact I. Nudelman at (781) 575-7695 or Regina S. Yeh (Senior Regulatory Affairs Associate) at (781) 575-7828 should you have any question. Thank you and we look forward to your expeditious review and approval of this application.

Sincerely,

  
I. Nudelman, RAC  
Director, Regulatory Affairs

Enclosure: Archival Copy (Blue folder): 1 copy  
Chemistry, manufacturing, and control copy (red folder): 1 copy

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

December 17, 1997

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER (HFD-600)  
Food and drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

AC  
NDA ORIG AMENDMENT

**Telephone Amendment  
Clotrimazole Vaginal Tablets, 100 mg  
ANDA # 73-249**

Dear Mr. Sporn:

Reference is made to our ANDA # 73-249 for Clotrimazole Vaginal Tablets, 100 mg, USP submitted April 17, 1989 and to the telephone discussion between Mr. Joseph Buccine of the Office of Generic Drugs and Regina S. Yeh, RAC of Copley Pharmaceutical, Inc., dated December 17, 1997.

During the telephone discussion, Mr. Buccine indicated that the Agency requests the addition of Microbial Limits as part of Copley's finished product release and stability specifications for Clotrimazole Vaginal Tablets, 100mg; as follows:

Microbial Limits:      USP  
                              Absence of indicator organisms  
                              Total microbial count \_\_\_\_\_

Copley agrees with the Agency's request. Accordingly, attached (Attachment 1) please find the revised finished product release and stability specifications which include the Microbial Limits specification. We are providing the Agency the response via fax to Mr. Buccine and followed by hard copies (Archival and CMC copies) via Federal Express mail service to your attention.

**RECEIVED**

DEC 18 1997

GENS

42



COPLEY PHARMACEUTICAL, INC.

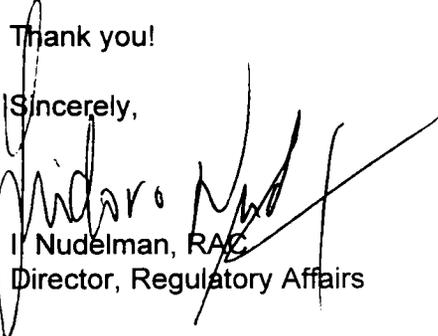
Response to Telephone Request  
Response to Telephone Request dated November 26, 1997  
Clotrimazole Vaginal Tablets 100mg  
ANDA# 73-249

page 2

We believe the information provided properly addresses your request. Please contact I. Nudelman at (781) 575-7695 or Regina S. Yeh (Senior Regulatory Affairs Associate) at (781) 575-7828 should you have any question.

Thank you!

Sincerely,

  
I. Nudelman, RAC  
Director, Regulatory Affairs

Attachments

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

January 13, 1998

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER (HFD-600)  
Food and drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AB

**Telephone Amendment  
Response to BioDivision Telephone Request dated January 5, 1998  
Clotrimazole Vaginal Tablets, 100 mg  
ANDA # 73-249**

Dear Mr. Sporn:

Reference is made to our ANDA # 73-249 for Clotrimazole Vaginal Tablets, 100 mg, USP submitted April 17, 1989 and to the telephone discussion among Ms. Nancy Chamberlin and Dr. Dale Conner of the Bioequivalence Division and Regina Yeh of Copley Pharmaceutical, Inc., dated January 5, 1998, as well as the telephone discussion among Ms. Chamberlin of Bioequivalence Division, I. Nudelman and Regina Yeh of Copley Pharmaceutical, Inc. on the same date.

During both telephone discussions, Ms. Chamberlin indicated that the Agency considers the dissolution specification of NLT \_\_\_\_\_ Q) in 30 minutes submitted to the Agency November 12, 1997 not acceptable. The Agency requests Copley to revise the dissolution specification as follows:

NLT (Q) = \_\_\_\_\_ in 30 minutes

Copley agrees with the Agency's request. Accordingly, attached (Attachment 1) please find the revised finished product release (QC95-171, dated 1/5/98) and stability specifications (QC87-171, dated 1/5/98) which include the revised dissolution specification. We are providing the Agency the response via fax to Dr. Conner and followed by hard copies (Archival, and Pharmacokinetic copies) via Federal Express mail service to your attention.

**RECEIVED**

JAN 14 1998

**GENERIC DRUGS**



**COPLEY PHARMACEUTICAL, INC.**

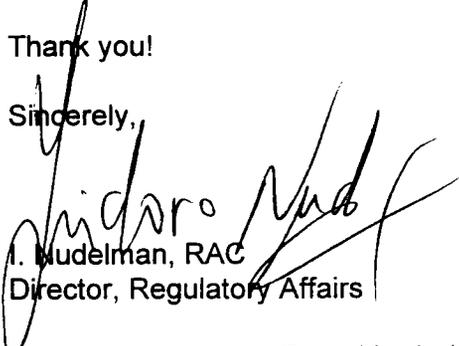
**Response to Telephone Request  
Response to Telephone Request dated January 5, 1998  
Clotrimazole Vaginal Tablets 100mg  
ANDA# 73-249**

page 2

We believe the information provided properly addresses the Agency's request. Please contact I. Nudelman at (781) 575-7695 or Regina Yeh, RAC (Senior Regulatory Affairs Associate) at (781) 575-7828 should you have any question.

Thank you!

Sincerely,

  
I. Nudelman, RAC  
Director, Regulatory Affairs

Enclosures: 1 Archival Copy (blue jacket)  
1 Pharmacokinetic Copy (orange jacket)

CC: Dale P. Conner, Pharm D  
Director of Division of Bioequivalence  
Food and drug Administration  
MPN II, Room E-130  
HFD-650  
7500 Standish Place  
Rockville, MD 20855



Draft Label & labeling need revision

5-11-93

Jerry Phillips

**Copley Pharmaceutical Inc.**

25 John Road  
Canton Commerce Center  
Canton, Massachusetts 02021  
(617) 821-6111

Fax:  
Canton (617) 821-4068  
Boston (617) 268-4394  
N.J. (201) 894-1553

N-000/AC

ANDA ORG AMENDMENT

Major Label

27 April 1993

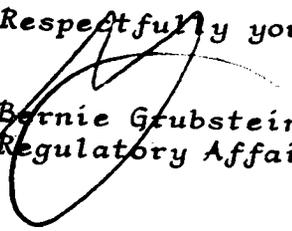
Roger L. Williams, M.D.  
Director  
Office of Generic Drugs (HFD-600)  
CDER, FDA  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

RE: CLOTRIMAZOLE VAGINAL TABLETS USP, 100mg  
ANDA 73-249  
AMENDMENT TYPE = MAJOR

Dear Dr. Williams:

Enclosed are Copley Pharmaceutical's responses to the deficiency comments listed in your division's notice of 15 January 1993, for our ANDA submission on Clotrimazole Vaginal Tablets USP, 100mg.

Respectfully yours,

  
Bernie Grubstein  
Regulatory Affairs

RECEIVED

APR 30 1993

GENERIC DRUGS

ORIGINAL

ANDA: 73-249

JAN 15 1993

Copley Pharmaceutical, Inc.  
Attention: Bernie Grubstein  
25 John Road  
Canton Commerce Center  
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated April 13, 1989, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Clotrimazole Vaginal Tablets USP, 100 mg.

Reference is also made to your amendments dated September 25, 1992 and December 7, 1992.

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

1. We await the final report of your bioequivalence studies for your product.

- 2.

---

the holder regarding its most recent status.

3. Please submit all current available room temperature stability data.

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

Sincerely yours,

1/17/93  
Rashmikant M. Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Copley  
Pharmaceutical  
Inc. BIOAVAILABILITY

25 John Road  
Canton Commerce Center  
Canton, Massachusetts 02021  
(617) 821-6111

Fax:  
Canton (617) 821-4068  
Boston (617) 268-4394  
N.J. (201) 894-1553

27 April 1993

Roger L. Williams, M.D.  
Director  
Office of Generic Drugs (HFD-600)  
CDER, FDA  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

OTDR NEW CORRES

RE: CLOTRIMAZOLE VAGINAL TABLETS USP, 100mg  
ANDA 73-249  
PHARMACOKINETIC STUDY RESULTS

Dear Dr. Williams:

Copley Pharmaceutical Inc., hereby provides the results of the clinical trials performed by whereby bioequivalency was determined for the Copley formulation of Clotrimazole Vaginal Tablets USP, 100mg to that of the listed brand formulation, Gyne-Lotrimin, manufactured by Schering Pharmaceutical.

Sincerely yours,

Beynte Grubstein  
Regulatory Affairs

RECEIVED

MAY 0 4 1993

GENERIC DRUGS

505(j)(2)(A)  
info is acceptable  
4/19/89  
Copley  
Pharmaceutical  
Inc.  
881 East First Street  
Boston, Mass. 02127  
(617) 268-1208

*Handwritten initials/signature*

13 April 1989

Marvin Seife, M.D.  
Director  
Division of Generic Drugs  
Office of Drug Standards  
Center for Drug Evaluation & Research  
HFN 230, Room 17-20B  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Dr. Seife:

Copley Pharmaceutical Inc., respectfully submits for your department's review its Abbreviated New Drug Application (ANDA) for Clotrimazole Vaginal Tablets, 100mg, in accordance with the guidelines listed in Section 505(j) of the Federal Food, Drug and Cosmetic Act.

A clinical study comparing our formulation to that of the brand, Gyne-Lotrimin Vaginal Tablets, 100mg, will be conducted by \_\_\_\_\_ . Results from that study will be provided under separate cover, as soon as they become available.

Sincerely yours,

*Handwritten signature of Bernie Grubstein*  
Bernie Grubstein  
Regulatory Affairs

RECEIVED

APR 17 1989

GENERIC DRUGS

ENCLOSURES: VOLUME 1 (1 of 1 in duplicate)  
Validation and Test Methods -- 3 copies (Separate Binder)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      73249**

**BIOEQUIVALENCE REVIEW(S)**

Clotrimazole  
100 mg vaginal tablet  
ANDA: 73-249  
Reviewer: Nhan L. Tran  
File: 732490.D97

Copley Pharmaceutical  
Canton, MA  
Submitted:  
March 13, 1992 & Sept 25, 1992  
April 27, 1993 &  
May 15, 1996 & June 25, 1996  
December 1, 1997.

### REVIEW OF AN AMENDMENT:

#### I. BACKGROUND:

The present submission (December 1, 1997) contains responses from the firm to the deficiencies from the Division of Chemistry of the Office of Generic Drugs. There is no information for the Division of Bioequivalence to review in this amendment. However, there is an amended specifications for the finished product and stability which includes the dissolution test (Paddle Method at 50 RPM in 900 ml 0.1N HCL and NLT of the labeled drug is dissolved in 30 minutes). (response #1). This is the dissolution specification that the Division of Bioequivalence has set in the review of October 23, 1997

#### II. RECOMMENDATION:

The dissolution specification incorporated in amended specification for the finished product and stability is acceptable to the Division of Bioequivalence.

Nhan L. Tran, Ph.D.  
Review Branch II  
Division of Bioequivalence

RD INITIALED SNERURKAR  
FT INITIALED SNERURKAR

Concur \_\_\_\_\_ Date 12/10/97  
Dale P. Conner, Pharm.D.  
Director  
Division of Bioequivalence

cc: ANDA #73-249 (original), HFD-655 (Tran, Nerurkar), Drug File, Division File.