

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

74-395

Generic Name: Miconazole Nitrate Vaginal Suppositories USP,
100 mg

Sponsor: L. Perrigo Company

Approval Date: March 20, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-395

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

APPROVAL LETTER

MAR 20 1997

L. Perrigo Company
Attention: David A. Jespersen
117 Water Street
Allegan, MI 49010



Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

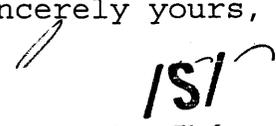
Reference is also made to your amendments dated December 14, 1995, March 21 and April 24, 1996, and March 7, 1997.

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

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

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

Sincerely yours,


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

for 3-20-97

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

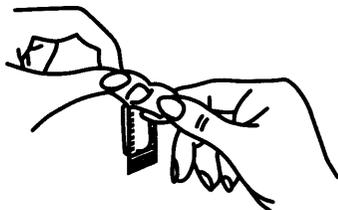
Final Printed Labeling

Final Printed Labeling Package Insert, Back ANDA 74-395

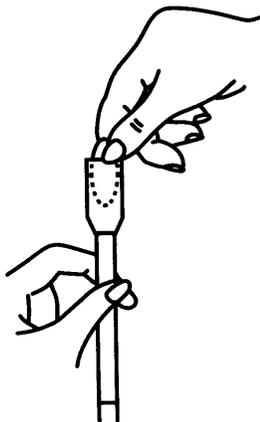
DIRECTIONS FOR USE

To begin the treatment, wait until bedtime. Before going to bed:

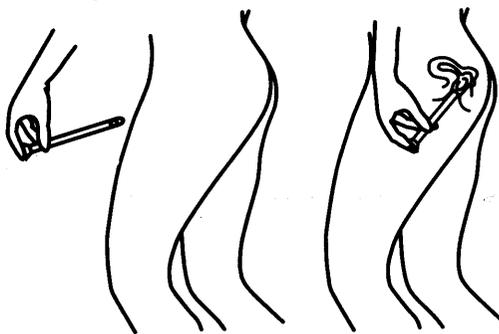
- 1** Tear off a single suppository. Separate the plastic wrap with your thumb. With thumb and forefinger on each hand, hold the plastic tabs and pull apart (see illustration).



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



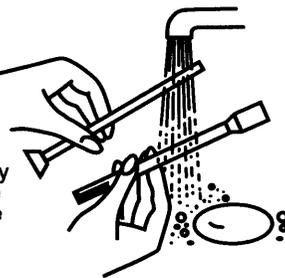
- 3** Hold the applicator containing the suppository by the opposite end from where the suppository is. Gently insert the applicator into the vagina as far as it will go comfortably. As shown in the pictures,



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 minipads or pantyshields during the time that you are using miconazole vaginal suppositories. This is because the suppository can leak and/or you may see some discharge. **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 as far as it will go.



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

ADVERSE REACTIONS (SIDE EFFECTS)

The following side effects have been reported with the use of miconazole vaginal suppositories: a temporary increase in burning, itching, and/or

irritation when the suppository is inserted. Abdominal cramping, headache, hives, and skin rash have also been reported. If any of these occur, stop using miconazole vaginal suppositories 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 a 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. Don't 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 INGREDIENT

miconazole nitrate (100 mg each suppository)

STORAGE

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

PERRIGO®
ALLEGAN, MI 49010 U.S.A. DIST.

APPROVED
REVISED 11/95

MAR 20 1997

**Final Printed Labeling
Suppository Containers
ANDA 74-395**

Miconazole Nitrate
Vaginal Suppository
USP, 100 mg
9 547 KO 00 XC

Miconazole Nitrate
Vaginal Suppository
USP, 100 mg
9 547 KO 00 XC

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Miconazole Nitrate
Vaginal Suppository
USP, 100 mg
9 547 KO 00 XC

MAR 20 1997
APPROVED

Final Printed Labeling
Package Insert, Front
ANDA 74-395

EDUCATIONAL BROCHURE
FULL PRESCRIPTION STRENGTH
MICONAZOLE NITRATE
VAGINAL SUPPOSITORIES USP, 100 mg
CURES MOST VAGINAL YEAST INFECTIONS

INDICATION

For the treatment of vaginal yeast infections (candidiasis).

If you have any or all of the symptoms of a yeast infection (vaginal itching, burning, discharge) and if at some time in the past your doctor has told you that these symptoms are due to a yeast infection, then miconazole vaginal suppositories should work for you. If, however, you have never had these symptoms before, you should see your doctor before using miconazole vaginal suppositories. **MICONAZOLE VAGINAL SUPPOSITORIES ARE FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS ONLY. THEY DO NOT TREAT OTHER INFECTIONS AND DO NOT PREVENT PREGNANCY.**

WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?

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

A yeast infection can occur at almost any time of life. It is most common during the childbearing years. The infection tends to develop most often in 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 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 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.

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, white vaginal discharge that may look like cottage cheese;
- Vaginal soreness, irritation or burning, especially during intercourse;
- Rash or redness around the vagina.

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

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast. Do not use in eyes or take by mouth.
- Do not use miconazole vaginal suppositories if you have any of the following signs and symptoms. Also, if they occur while using miconazole vaginal suppositories, STOP using the product and contact your doctor right away. You may have a more serious illness.
Fever (Above 100°F orally)
Pain in the lower abdomen, back or either shoulder
A vaginal discharge that smells bad

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

CONTENTS

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

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

APPROVED

MAR 20 1997

Final Printed Labeling
Carton
ANDA 74-395

MAR 20 1997

APPROVED

MICONAZOLE NITRATE
VAGINAL SUPPOSITORIES USP, 100 mg

CURES MOST VAGINAL YEAST INFECTIONS

MICONAZOLE NITRATE

VAGINAL SUPPOSITORIES USP, 100 mg

CURES MOST VAGINAL YEAST INFECTIONS

FULL PRESCRIPTION STRENGTH

MICONAZOLE NITRATE

VAGINAL SUPPOSITORIES USP, 100 mg

CURES MOST VAGINAL YEAST INFECTIONS

7 VAGINAL SUPPOSITORIES

ACTIVE INGREDIENT: miconazole nitrate (100 mg each suppository).
INACTIVE INGREDIENTS: hydrogenated vegetable oil base.
Store at room temperature 15-30°C (59-86°F).
Avoid heat (over 30°C or 86°F).
See end flap for lot number and expiration date.



3 647 12 PO A

Now you can buy miconazole nitrate vaginal suppositories without a prescription. They are a cure for most vaginal yeast infections.

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

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

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

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

WARNINGS: DO NOT USE MICONAZOLE NITRATE VAGINAL SUPPOSITORIES IF YOU HAVE ANY OF THE FOLLOWING SIGNS AND SYMPTOMS. ALSO, IF THEY OCCUR WHILE USING MICONAZOLE NITRATE VAGINAL SUPPOSITORIES, 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). These suppositories contain hydrogenated vegetable oil. Hydrogenated vegetable oil may weaken latex in condoms or in diaphragms. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using MICONAZOLE NITRATE VAGINAL SUPPOSITORIES. • Do not use tampons while using this medication. • DO NOT USE IN GIRLS LESS THAN 12 YEARS OF AGE. • If you are pregnant or think you may be pregnant, do not use this product except under the advice and supervision of a doctor. • Keep this and all drugs out of the reach of children. • In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

IMPORTANT: SUPPOSITORIES ARE INDIVIDUALLY SEALED IN PRINTED PLASTIC FOR YOUR PROTECTION. IF A PLASTIC UNIT IS BROKEN OR IF THERE ARE SIGNS OF TAMPERING, DO NOT USE. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

PERRIGO ALLEBAN, MI 48010 U.S.A. DIST

**1 page redacted from this
section of the approval package
consisted of draft labeling**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

MEDICAL REVIEW

File: 74-395

Division of Anti-Infective Drug Products

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

FACSIMILE TRANSMISSION

DATE: 4.18.96 Number of Pages (including cover sheet) 4

TO: Virginia K. Green

COMPANY: Regulatory Affairs
FAX # 616-673-7655

FAX NUMBER: Perrigo

MESSAGE: FYI

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

FROM: Julius Piver, M.D.
Medical Officer

TITLE: HFD 520

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

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ANDA 74-395

CLINICAL OUTCOME - PER MEDICAL OFFICER

Table 8

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
Perrigo		
Ortho		

Table 8a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
Perrigo		
Ortho		

Table 8b

Therapeutic Cure Rate

Treatment Group	Visit 3
Perrigo	
Ortho	

APPEARS THIS WAY ON ORIGINAL

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

August 29, 1995

**COMPARISON OF MICONAZOLE 100 MG SUPPOSITORIES (FERRIGO) AND
MONISTAT-7® (ORTHO) IN THE TREATMENT OF VULVO-VAGINAL CANDIDIASIS**

PROTOCOL 801369

Clinical Cure Rates

No. of Patients/Total No. of Evaluable Patients (%)		
Treatment Group	Improvement of Symptoms Visit 2	No symptoms Visit 3
Ferrigo	68/68 (100%)	55/64 (85.84%)
Ortho	61/62 (98.39%)	56/60 (93.33%)
p-value	N/A	0.179

APPEARS THIS WAY
ON ORIGINAL

August 28, 1995

**COMPARISON OF MICONAZOLE 100 MG SUPPOSITORIES (PERRIGO) AND
MONISTAT-7® (ORTHO) IN THE TREATMENT OF VULVO-VAGINAL CANDIDIASIS****PROTOCOL 901366****Visit Specific Mycological Cure Rates**

Treatment Group	No. of Patients/Total No. of Evaluable Patients (%)	
	Mycological Cure Visit 2	Mycological Cure Visit 3
Perrigo	82/68 (81.18%)	80/83 (79.37%)
Ortho	58/82 (83.55%)	48/80 (80.00%)
p-value	0.612	0.930

The Visit 3 mycological data is independent of Visit 2 mycological data.

APPEARS THIS WAY
ON ORIGINAL

DATE SUBMITTED:	AUGUST 4, 1993
DATE RECEIVED:	SEPTEMBER 3, 1993
DATE OF AMENDMENT:	NOVEMBER 16, 1994
DATE OF ORIGINAL REVIEW:	DECEMBER 5, 1995
DATE OF AMENDMENT:	MARCH 21, 1996
DATE REVIEW BEGUN:	JULY 18, 1996
DATE FIRST DRAFT COMPLETED:	AUGUST 15, 1996
DATE RETURNED TO MO:	OCTOBER 8, 1996
DATE FINAL COMPLETED:	OCTOBER 22, 1996

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

ANDA 74-395

Requested By: Office of Generic Drugs
HFD-600

Applicant: L. Perrigo Co.
117 Water Street
Allegan, Michigan 49010

Drug: Miconazole Nitrate Vaginal Suppository, 100 mg

Drug Category: Anti-fungal

Dose Form: Vaginal suppository

Dosage: One 100 mg suppository inserted into the vagina nightly for seven consecutive nights

Materials Reviewed: ANDA 74-395 submission (000) - 9 volumes
ANDA 74-395 amendment (3/21/96) - 1 volume

Purpose:

The purpose of this ANDA is to obtain market approval of a generic form of miconazole nitrate vaginal suppository manufactured by L. Perrigo Co. for the treatment of recurrent vaginal candidiasis. The Applicant has conducted a study comparing the efficacy and safety of miconazole 100 mg vaginal suppository with that of Monistat-7® 100 mg vaginal suppository in the treatment of women with vaginal candidiasis.

Background:

Most of the commercially available drugs for the topical treatment of vulvovaginal candidiasis are either polyenes such as nystatin or imidazoles such as clotrimazole, miconazole, terconazole, and others. These agents are available in a variety of preparations including vaginal creams and vaginal suppositories.

Miconazole is a synthetic imidazole derivative that is fungicidal *in vitro* against species of the genus *Candida*. It was first approved for use in vulvovaginal candidiasis as a prescription vaginal cream for daily use in a 7-day regimen in 1973 (Monistat-7® Vaginal Cream), then as a prescription vaginal suppository for daily use in a 7-day regimen in 1980 (Monistat-7® Vaginal Suppositories).

In 1990, the Fertility and Maternal Health Advisory Committee of the FDA concluded that vulvovaginal candidiasis could be safely and adequately self-treated by the consumer, and that the 7-day treatment regimens of miconazole and clotrimazole could be approved for over-the-counter use in non-pregnant women with self-recognized vulvovaginal candidiasis. Miconazole nitrate vaginal suppositories for the 7-day treatment of vulvovaginal candidiasis was approved for over-the-counter use in 1991.

The Applicant desires to make available to the consumer its generic preparation of miconazole 100mg vaginal suppository which they believe to be comparable in safety and efficacy to the presently marketed Monistat-7 (Ortho) 100mg suppository.

Original review of this application was completed in December 1995. At this time it was determined by the original reviewing Medical Officer (MO) that, while the Applicant's submission found 130 patients evaluable, the MO found 19 of these 130 unevaluable because they failed to return for follow-up within acceptable time intervals. This was communicated to the Perrigo Company in an Agency communication dated February 23, 1996. Upon internal review, the Applicant found that there was a programming error in a summary table previously submitted. This table had incorrectly documented return visit dates for several patients. On March 21, 1996 the Applicant submitted corrected summary tables from which the Applicant documented 126 evaluable patients. The present reviewing MO analyzed the corrected summary tables which were verified by reference to the case report forms included in the original submission.

Clinical Studies:

One clinical study (protocol number 901368) was conducted by the Applicant in an attempt to demonstrate bioequivalence between a generic miconazole 100 mg vaginal suppository administered once daily for seven days (Perrigo) and the approved preparation Monistat-7®, miconazole 100 mg vaginal suppository administered once daily for seven days (Ortho).

Protocol 901368

Title: Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7® (Ortho) in the Treatment of Vulvovaginal Candidiasis

Study Design: The study was a randomized (1:1), double-blinded, multi-center, controlled, parallel group study conducted at nine clinical sites in the provinces of Quebec and Ontario, Canada. Patients with symptomatic *Candida* vaginitis were randomly assigned to receive either miconazole 100 mg vaginal suppository (Perrigo) once daily for seven days or Monistat-7® miconazole 100 mg vaginal suppository (Ortho) once daily for seven days.

Monitoring: The study was conducted in accordance with the "Guidelines on Research Involving Human Subjects" (Medical Research Council of Canada, 1987). Regular monitoring visits were made to each study center by _____, who established that the protocol was being followed and that data were being collected accurately. At the conclusion of the study, unused study medications were retained and stored with permanent study files by _____

Protocol Overview:

After giving written informed consent, each patient had a medical history taken and physical examination performed. Specimens of vaginal discharge were taken for microscopic examination of a KOH wet mount and for mycologic culture. The patients were seen for a total of three visits. The entry visit (V1), first post-treatment visit (V2), and second post-treatment visit (V3). Upon entry, each patient was given a diary in which to record her symptoms daily until the final visit.

The first post-treatment visit was scheduled 14 days after the entry visit. This was seven days after completion of a seven day treatment regimen, or day 14 of the study. The Applicant allowed an interval of 7-10 days after treatment to accommodate weekends and holidays (study days 14-17). At that time the patient was evaluated again for signs and symptoms of candida vaginitis and by KOH wet mount and fungal culture of vaginal discharge. Clinical and mycologic responses were recorded for each patient. At this visit, patients were also questioned by the investigator concerning possible adverse drug effects. Patients found to have positive KOH prep or positive fungal culture at the first post-treatment visit were recorded as treatment failures and did not return for the second post-treatment visit.

The second post-treatment visit was scheduled 23 days after the first post-treatment visit. The Applicant allowed an interval of 31-34 days post-treatment to accommodate weekends and holidays (study days 38-41). At that time the patient was evaluated again for signs and symptoms of candida vaginitis and by KOH wet mount and fungal culture of vaginal discharge. Clinical and mycologic responses were recorded for each patient. At this visit, patients were again questioned by the investigator concerning possible adverse drug effects.

MEDICAL OFFICER COMMENT: The reviewing Medical Officer (MO) found the manner in which V3 (the second post-treatment visit) was scheduled (23 days after V2) to be inconsistent with the Applicant's stated intent. The Applicant planned to evaluate patients at a second post-treatment visit at an interval 31-34 days after completion of a 7-day treatment (study days 38-41), which is fully consistent with Agency guidelines as stated in the Guidance for the Performance of a Bioequivalence Study for Vaginal Antifungal Products, February, 1990. However, for patients who presented early or late for V2 (i.e. outside of the interval of study days 14-17), a V3 scheduled at a fixed interval from V2 could also then be early or late, possibly making the patient ineligible for evaluation (e.g. the patient who presented for V2 at study day 20 would be scheduled for V3 at study day 43, which is outside of the interval of study days 38-41). The effect this practice had on the number of evaluable patients will be discussed below.

Inclusion Criteria: To be included in the study patients had to fulfill these inclusion criteria:

- Informed written consent of the patient: Patients were entered into the study only after reading, understanding, and signing an informed consent. Patients were supplied with the name and telephone number of a physician to call in the event of an adverse reaction.
- Patients had to be otherwise healthy females with at least one of the following clinical symptoms or signs of vaginal candidiasis: itching, burning/irritation, vulvar erythema, edema or excoriations and/or vaginal erythema or edema.
- Positive KOH smear and culture for *Candida albicans* within one week of start of the treatment.
- Patients must not be expected to begin menstruation during the treatment period. KOH and culture were repeated if treatment start was delayed more than 7 days.
- Sexually active patients must use a reliable method of birth control.
- Patients must agree to abstain from douches, tub baths, swimming, sexual intercourse and other activities likely to alter the disposition of drug in the vagina during treatment.
- Sexual intercourse following the treatment period must involve the use of a condom.

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

- Recurrent vaginal infections resistant to standard treatment
- Pregnancy or lactation-urine pregnancy test performed at intake
- Coexisting sexually transmitted disease

-
- Known sensitivity to imidazole antifungal agents
 - Any significant chronic illness
 - Symptoms of infection other than candidiasis
 - Non-compliant behavior
 - Use of any systemic anti-infectives, anti-mycotics, corticosteroids, or immunosuppressive drugs within 7 days prior to entry
 - Use of any vaginal douches or feminine sprays within the 48 hours prior to entry
 - Any anatomical anomaly likely to affect therapeutic efficacy of the test medications

MO COMMENT: The MO agrees with the inclusion and exclusion criteria used in the protocol.

Evaluability Criteria:

Visit 2 (First post-treatment visit)

To be considered evaluable for the first post-treatment visit by the Applicant, patients had to have met all inclusion and exclusion criteria. They had to have returned for the first post-treatment visit within an interval of 7-10 days following completion of treatment (study days #14-17).

MO COMMENT: The reviewing MO found fewer patients evaluable at this visit than did the Applicant. The MO extended the interval allowable for the first post-treatment visit to allow for weekends and holidays, based on Agency precedent. Thus patients who presented for visit 2 any time between 6 and 11 days following treatment (study days #13-18) were deemed evaluable by the MO. However, review of the line listings provided by the Applicant in the communication of 3/21/96 revealed that the number of days between visits 1 and 2 were counted incorrectly. When compared with the clinical data sheets, it was found that the interval between these two visits was recorded on the line listings as one day longer than it actually was. When this error was corrected and the extended interval for follow-up applied, 16 patients were rendered unevaluable because of presenting too early or too late for follow-up. These were patients numbered 2, 40, 52, 69, 74, 75, 80, 82, 83, 91, 92, 93, 94, 112, 138, 172. The list of patients considered ineligible for evaluation by the Applicant was reviewed by the Medical Officer for patients rendered evaluable by the extended interval for follow-up visits. None was found.

Clinical evaluations were made by taking a history and performing a physical examination of the affected area. The parameters evaluated were erythema, discharge, itching, and burning. The severity of vulvar and/or vaginal irritation was evaluated on a scale of 0-3 as follows:

- 0-no symptoms
- 1-mild itching and burning
- 2-moderate itch, some swelling and erythema
- 3-severe itch, erythema, swelling, presence of pustules, excoriations and fissuring.

Mycologic evaluations were also made at each visit. Specimens of vaginal discharge were sent for fungal culture, and separate specimens of vaginal discharge were examined microscopically using KOH wet mount to look for fungal forms.

Visit 3 (Second post-treatment visit)

To be considered evaluable for the second post-treatment visit by the Applicant, patients had to have returned for the visit within an interval of 31-34 days following completion of treatment (study days # 38-41).

MO COMMENT: The reviewing MO found fewer patients evaluable at this visit than did the Applicant. The MO extended the interval allowable for the second post-treatment visit to allow for weekends and holidays, based on Agency precedent. Thus patients who presented for visit 3 any time during the interval 27-36 days following treatment (study days #34-43) were evaluable. Only one patient, number 112, did not present for visit 3 within this interval, but was already considered unevaluable because of late presentation for visit 2. The list of patients considered ineligible for evaluation by the Applicant was reviewed for patients rendered evaluable by the extended interval for follow-up visits. None was found.

Clinical and mycologic evaluations were similar to those used at visit 2.

Endpoints:

A clinical cure was defined by the Applicant as an improvement in clinical symptoms (lower score on the scale of 0-3 described above) at visits 2 and 3 or an absence of symptoms at visit 3.

Mycologic eradication was defined by the Applicant as negative KOH prep and negative fungal culture at both visits 2 and 3. A positive KOH prep or a positive fungal culture at either visit 2 or 3 was considered a mycologic failure.

An overall (therapeutic) cure was defined by the Applicant as both clinical and mycologic cure. A therapeutic failure was any patient who was a clinical or mycological failure at any follow-up visit.

MO COMMENT: The reviewing Medical Officer considered that specimens which revealed fungal forms on KOH prep but that did not grow when cultured might be exhibiting dead organisms on microscopic examination. For this reason, specimens that were KOH positive but culture negative were scored as mycologic cures. Clinical and mycological cure rates were considered secondary efficacy variables. The primary efficacy variable was the therapeutic cure rate.

Safety Evaluations:

Patients were asked to report any adverse reactions to the study treatment on an Adverse Event Form. The examining physician noted any adverse events reported spontaneously by the patient or elicited at the time of questioning and attributed to the miconazole treatment.

Study Results:

Evaluable Patients: This study was conducted at nine clinical sites in the provinces of Quebec and Ontario, Canada by nine qualified investigators (6 gynecologists and 3 general practitioners). A total of 159 patients were enrolled. Eighty-two were randomized to receive the Perrigo miconazole 100mg vaginal suppository, and 77 were randomized to receive the Ortho Monistat-7® vaginal suppository. The investigators, their geographical locations, and the number of enrolled and evaluable patients are shown in Table 1 as submitted by the Applicant. These figures reflect reanalysis of the number of evaluable patients based on the Applicant's amendment dated 3/21/96.

The Applicant considered 126 patients evaluable. Table 2 presents these data as analyzed by the reviewing Medical Officer, who found 110 patients evaluable. Below each table is the number of patients that was excluded with the reasons for exclusion. The Medical Officer identified 16 additional patients (8 Perrigo, 8 Ortho) who presented for follow-up too late or too early. The criteria for making these exclusions are presented in detail above, in the section Evaluability Criteria. The patients excluded by the reviewing MO are listed below:

APPEARS THIS WAY
ON ORIGINAL

PATIENT NO.

VISIT VIOLATION

(anticipated interval = 13-18 days)

2	visit 2; 12 days
40	visit 2; 11 days
52	visit 2; 19 days
69	visit 2; 19 days
74	visit 2; 19 days
75	visit 2; 19 days
80	visit 2; 19 days
82	visit 2; 12 days
83	visit 2; 12 days
91	visit 2; 10 days
92	visit 2; 21 days
93	visit 2; 21 days
94	visit 2; 19 days
112	visit 2; 20 days
138	visit 2; 20 days
172	visit 2; 12 days

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 1
Patient Evaluability by Investigator/Center
Applicant Analysis

Investigator	Miconazole 100mg Perrigo			Monistat ®Ortho		
	Enrolled	Evaluable	% Eval	Enrolled	Evaluable	% Eval
	14	10	71.4	14	9	64.3
	14	14	100.0	14	12	85.7
	14	13	92.9	14	14	100.0
	14	14	100.0	12	11	91.7
	12	8	66.7	12	5	41.7
	9	6	66.7	8	7	87.5
	2	1	50.0	2	1	50.0
	3	0	0.0	0	0	0.0
	0	0	0	1	1	100.0
Total	82	66	80.5	77	60	77.9

Reasons for Exclusion by Applicant:

	Perrigo	Ortho
Negative culture on admission	5	9
Protocol violation	0	1
Lost to follow-up or missing data		
Came to visit 1 only	3	2
Came to visits 1 and 2 only	4	0
Adverse Drug Reaction	1	0
Came too late for visit 2 or 3	3	5
Total	16	17

TABLE 2
Patient Evaluability by Investigator/Center
Medical Officer Analysis

Investigator	Miconazole 100mg Perrigo			Monistat Ortho®		
	Enrolled	Evaluable	% Eval	Enrolled	Evaluable	% Eval
[REDACTED]	14	05	35.7	14	4	28.6
[REDACTED]	14	13	92.8	14	12	85.7
[REDACTED]	14	12	85.7	14	14	100.0
[REDACTED]	14	14	100.0	12	11	91.7
[REDACTED]	12	7	58.3	12	5	41.7
[REDACTED]	9	6	66.7	8	5	62.5
[REDACTED]	2	1	50.0	2	1	50.0
[REDACTED]	3	0	0.0	0	0	0.0
[REDACTED]	0	0	0	1	0	0.0
Total	82	58	70.7	77	52	67.5

Reasons for Exclusion by Medical Officer:

	Perrigo	Ortho
Negative culture on admission	5	9
Protocol violation	0	1
Lost to follow-up or missing data		
Came to visit 1 only	3	2
Came to visits 1 and 2 only	4	0
Adverse Drug Reaction	1	0
Came too early or too late for visit 2 or 3	11	13
Total	24	25

Demographics: Demographic data were provided by the Applicant. There was no significant difference between the two treatment groups as shown in Table 3 below.

TABLE 3
Demographic Data

	Perrigo N=68	Ortho N=62
Age (yrs)		
Range	16-63	15-65
Mean	31	32
Height (cm)		
Range	152-183	140-180
Mean	163	161
Weight (kg)		
Range	45-109	45-86
Mean	61	60

MO COMMENT: The patients were not classified by race.

Efficacy:

According to the Applicant, clinical and mycologic cure rates were based on assessments made at visits 2 and 3. Therapeutic cure rates, by definition, were based on assessments that could only be made at visit 3. These are all presented below in Table 4. Patients who were considered a treatment failure at visit 2 did not return for further evaluation at visit 3. These patients were not counted among the number evaluated at visit 3, and therefore the number of patients evaluated at visit 3 is smaller than the number evaluated at visit 2 in both treatment groups.

APPEARS THIS WAY
ON ORIGINAL

Of the 159 patients who received therapy, 126 were considered evaluable for efficacy at V2 by the Applicant. (See Table 1.) Sixty-six of these patients received miconazole 100mg vaginal suppository (Perrigo), and 60 received Monistat-7 (Ortho). The reviewing Medical Officer excluded 16 patients because of failure to present for follow-up within the extended intervals permitted in the evaluation of vaginal antifungal products, and therefore considered 110 patients evaluable for efficacy. (See Table 2.) Fifty-eight of these patients received miconazole 100 mg vaginal suppository (Perrigo), and 52 received Monistat-7®.

Patients who were considered treatment failures at visit 2 were not included in the number of evaluable patients at visit 3 in the Applicant's report of results. The reviewing Medical Officer determined that such patient were evaluable at visit 3. The Medical Officer otherwise concurred with the scoring of cures and treatment failures as reported in the 3/21/96 line listings provided by the Applicant.

Clinical cure rates reported by the Applicant for visit 2 were 100% for the Perrigo product and 98.4% for the Ortho product. (See Table 4.) Analysis by the Medical Officer found clinical cure rates of 100% for both treatment groups at visit 2. (See Table 5.) For visit 3, the Applicant demonstrated clinical cure rates of 85.9% (Perrigo) and 93.3% (Ortho). The Medical Officer's analysis yielded 84.5% (Perrigo) and 94.2% (Ortho).

Mycologic cure rates at visit 2 reported by the Applicant were 91.2% for the Perrigo product and 93.5% for the Ortho product. Visit 2 mycologic cure rates determined by the Medical Officer were 93.1% (Perrigo) and 96.2% (Ortho). At visit 3, the Applicant found mycologic cure rates of 79.4% (Perrigo) and 80.0 (Ortho). Medical Officer analysis yielded visit 3 mycologic cure rates of 77.6% (Perrigo) and 78.8% (Ortho).

Therapeutic cure rates reported by the Applicant were 70.6% for the Perrigo treatment group and 75.8% for the Ortho treatment group. Therapeutic cure rates determined by the Medical Officer were 72.4% (Perrigo) and 76.8% (Ortho).

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 4
CURE RATES PER APPLICANT

Treatment Group	Perrigo			Ortho		
	# cure	#evaluated	%	# cure	#evaluated	%
Clinical Cure (%)						
visit 2	68	68	100	61	62	98.4
visit 3	55	64	85.9	56	60	93.3
Mycologic Cure (%)						
visit 2	62	68	91.2	58	62	93.5
visit 3	50	63	79.4	48	60	80.0
Therapeutic Cure (%)						
visit3	48	68	70.6	47	62	75.8

According to the MO, clinical and mycologic cure rates were based on assessments made at visits 2 and 3. Therapeutic cure rates, by definition, were based on assessments that could only be made at visit 3. These are all presented below in Table 5. Patients who were considered a treatment failure at visit 2 did not return for further evaluation at visit 3. The Medical Officer determined that these patients should be counted in the number evaluated in both visits 2 and 3, since they are fully evaluable, but, having failed treatment, did not need to present for the test-of-cure visit. Thus the number of patients evaluated at visit 3 is the same as the number evaluated at visit 2; consequent changes in cure rates are reflected below (see Table 5). The Medical Officer otherwise concurred with the scoring of cures and treatment failures as reported in the line listings provided in the March 21, 1996 amendment and compared with the case report forms provided by the Applicant.

APPEARS THIS WAY
ON ORIGINAL

TABLE 5
CURE RATES PER MEDICAL OFFICER

Treatment Group	Perrigo			Ortho		
	# cure	#evaluated	%	# cure	#evaluated	%
Clinical Cure (%)						
visit 2	58	58	100.0	52	52	100.0
visit 3	49	58	84.5	49	52	94.2
Mycologic Cure (%)						
visit 2	54	58	93.1	50	52	96.2
visit 3	45	58	77.6	41	52	78.8
Therapeutic Cure (%)						
visit3	42	58	72.4	40	52	76.9

Safety: Two patients reported one adverse event each. One of these patients (Perrigo 9) withdrew from the study. Adverse event data are summarized below in Table 6.

TABLE 6
ADVERSE EVENTS

Patient no. (Treatment Group)	Symptoms	Visit	Related to Medication? (Investigator's Assessment)
9 (Perrigo)	Redness, vulvar swelling, acute burning; withdrew	2	Yes
112 (Ortho)	Itching	2	Uncertain

Summary:

This was a randomized (1:1), double blinded, multi-center, controlled, parallel group study undertaken to evaluate the safety and efficacy of a generic form of miconazole 100mg vaginal suppository manufactured by the L. Perrigo Co. given for 7 days for the treatment of recurrent vaginal candidiasis. The comparative treatment regimen was Monistat-7® miconazole 100 mg vaginal suppositories manufactured by Ortho Pharmaceutical Corp. given for seven days. One hundred fifty-nine patients with clinical evidence of vulvovaginal candidiasis were enrolled and randomly assigned to treatment.

The data submitted by the Applicant have been verified and reanalyzed by the reviewing Medical Officer with statistical consultation from the Division of Biometrics. The consult is attached. The criterion for demonstrating therapeutic equivalency for generic drugs is that the upper and lower limits of the 90% confidence interval of the difference between the two active products be within the interval ± 0.20 . With the exception of the clinical cure rates at visit 3, all of the 90% confidence intervals for the secondary efficacy variables of clinical cures and mycological cures were within the interval ± 0.20 .

At V2, the clinical cure rates for both the Perrigo and Ortho products were 100%, thus the 90% CIs meet the Generic Drug equivalency criterion of ± 0.20 . At V3, the Perrigo versus Ortho 90% CI is $\{-21\%, 15.3\%\}$. The V2 mycologic cure rate 90% CI for Perrigo versus is $\{-11.9\%, 5.8\%\}$. The V3 mycologic cure rate 90% CI is $\{-16\%, 13.5\%\}$.

The 90% confidence interval for the primary efficacy variable of therapeutic cure also met the generic drug equivalency criterion of ± 0.20 . The V3 therapeutic response 90% CI for Perrigo versus Ortho is $\{-19.9\%, 10.9\%\}$.

APPEARS THIS WAY
ON ORIGINAL

Conclusion: The formulations of miconazole nitrate 100 mg vaginal suppository manufactured by the L. Perrigo Co. and by Ortho Pharmaceuticals Corp. are equivalent in safety and efficacy for the treatment of vulvovaginal candidiasis for seven days.

Recommendation: I recommend approval of ANDA 74-395.

/s/
Andrea Meyerhoff MD MSc DTMH
Medical Officer

cc: ANDA 74-395
HFD-600/
HFD-520/
HFD-520/Meyerhoff

Concurrence Only:
HFD-520/DivDir/Feiga.
HFD-520/MTL/Leissa

12-20-86
/s/ 27/92

APPEARS THIS WAY
ON ORIGINAL

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APPEARS THIS WAY
ON ORIGINAL

Rational for Expedited Review

The Perrigo Company respectfully requests expedited review of this major deficiency response for the following reasons:

1. The Agency has far exceeded the statutory requirement of 180 days for review of this application. The bioequivalence review of this application has been with the Agency for approximately 900 days; ~~the initial review for the bioequivalence study was with the Agency over 800 days before completion and then more than 100 days for the preparation and approval of the deficiency letter.~~
2. To the Perrigo Company's understanding, the initial clinical and statistical review of the biostudy was complete on or about ~~November 9, 1995.~~ However, a deficiency letter did not issue to the Perrigo Company until February 23, 1996 (over 100 days later). Dec 5, 96
3. The Agency's 02/23/96 letter did not indicate the patients the Agency was excluding from the study and therefore the Perrigo Company could not begin to formulate a response to the Agency's comments until the Agency's personnel had returned from vacation (on or about March 1) and the patient numbers could be obtained.
4. ~~The discrepancy in the number of evaluable patients has been found to be mostly from an error in the tables the Agency had requested previously in a telephone amendment to the application. If the Agency had notified the Perrigo Company earlier via telephone, the error in the tables could have been corrected via a telephone amendment.~~
5. The delays the Agency has incurred in the review of this application, including the bioequivalence study, has created an undue economic hardship for the Perrigo Company. This is not due to Perrigo's timing in responding back to the Agency on issues, but due to the Agency's delay in review of the application.

APPEARS THIS WAY
ON ORIGINAL

COMMENT 1: The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo-group and 55 in the Ortho-group).

what are those?

see
Evaluability
Criteria for
Vag Candid

RESPONSE: Data from the 19 excluded patients indicated by Dr. Gross in a fax received by _____ on March 7, 1996 have been reviewed. During the data review, a programming error was discovered in a summary table, previously requested by the Agency, by which some of the intervals between visits were out by 1 week. Consequently, there are only 4 patients which will be excluded according to the Agency's criteria. Attached is a listing of the actual visit dates for the 19 patients, with the 4 excluded patients indicated, as well as revised summary tablets.

7
28cl. p rx

28cl. p rx

what was said in def letter

In the original analysis, which demonstrated equivalent efficacy for the two products, patients who returned over a week late for the first return visit (Visit 2) were excluded. It was felt that late returns for the second follow-up visit (Visit 3) bias the data only against the test formulations since there is increased risk of re-infection the longer the time between treatment and Visit 3, thus patients up to two weeks late were included.

Using the Agency's criterion of excluding any patient who returned more than a week late for a visit (n=4), the confidence intervals have been re-calculated. Revised data are presented in the attached Tables 2a, 2b, 3 and 4. It can be seen that the conclusions drawn in the original report remain unchanged.

APPEARS THIS WAY
ON ORIGINAL

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

<u>Group</u>	<u>Visit 2</u> <u>Agency (Perrigo)</u>	<u>Visit 3</u> <u>Agency (Perrigo)</u>
<u>Mycological Cure Rate</u>		
Perrigo	51/56 (62/68)	40/56 (50/63)
Ortho	52/55 (58/62)	44/55 (48/60)
<u>Clinical Cure Rate</u>		
Perrigo	55/56 (68/68)	47/56 (55/64)
Ortho	54/55 (61/62)	50/55 (56/60)
<u>Therapeutic Cure Rate</u>	<u>Visit 3 Agency (Perrigo)</u>	
Perrigo	40/56 (48/68)	
Ortho	43/55 (47/62)	

RESPONSE: Please see response to Comment 1.

COMMENT 3: The Agency evaluated the data based on 111 evaluable subjects as summarized above and concluded that:

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

RESPONSE: Please see response to Comment 1.

APPEARS THIS WAY
ON ORIGINAL

COMMENT 4: The summary report, IRB approval letter, drug composition statement, nor the product formulation data documented the product Lot number used in the study. The lot numbers, 2T6450 for the test and 22A125 for Ortho product were recorded only in the protocol. In future the Lot numbers of products used should be properly recorded on all forms.

RESPONSE: The Perrigo Company acknowledges that the Lot Numbers of products used should be properly recorded on appropriate forms including the summary report. However, the IRB approval letter is not specific to certain lot numbers for either product, it is only required to be specific for the project. The drug composition statement found on page 52 of the ANDA document is for product manufactured under this formula, not just the batch manufactured for the bioequivalence study. As for the product formulation data, the manufacturing order for the batch made for the bioequivalence study begins on page 204 of the ANDA document and includes the batch no. 2T6450, which in this case is also considered the lot number. Please see page 469 of the ANDA document for an explanation of Perrigo's formula and control numbers.

APPEARS THIS WAY
ON ORIGINAL

These coincide with data in NDA

PROJECT 901368

PATIENT VISIT DATES FOR 19 PATIENTS EXCLUDED BY FDA

Treatment Group: Perrigo

(14) protocols are 14-17

23d

protocols are 35-42
35-42-3571

Patient No.	Visit 1		Visit 2		Visit 3	
22*	20/10/92	28d	16/11/92	14	30/11/92	= 42d
42	08/09/92	15	22/09/92	27d	14/10/92	= 37d
45	24/09/92	15	08/10/92	25d	02/11/92	= 40d
47	01/10/92	15	15/10/92	25	09/11/92	= 40
122	20/10/92	17	05/11/92	21	26/11/92	= 38
129	11/11/92	15	25/11/92	23	18/12/92	= 38
134	23/11/92	15	07/12/92	25	04/01/93	= 41
→ 138	15/12/92	21	04/01/93	22	26/01/93	= 43
152*	16/02/93	16	03/03/93	34d	06/04/93	= 50
158	18/01/93	15	01/02/93	23d	24/02/93	= 38
163	23/03/93	15	06/04/93	25d	29/04/93	= 40
165	01/04/93	15	15/04/93	25d	10/05/93	= 40

Treatment Group: Ortho

Patient No.	Visit 1		Visit 2		Visit 3	
24*	12/01/93	15	26/01/93	35d	02/03/93	= 50
→ 112	22/12/92 ⁹²	21	11/01/93	24	03/02/93	= 45
141	23/12/92	15	06/01/93	26	01/02/93	= 41
151*	11/12/92	21	31/12/92	26	05/02/93	= 57
160	21/01/93	15	04/02/93	28	01/03/93	= 40
164	24/03/93	15	07/04/93	27	29/04/93	= 37
168	18/03/93	15	01/04/93	21	22/04/93	36

* excluded from March 1996 re-analysis

APPEARS THIS WAY
ON ORIGINAL

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368

All eligible enrolled patients, by treatment group

BASELINE

1ST VISIT

2ND VISIT

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
1	Pos	Pos	Moderate	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	36
2	Pos	Pos	Moderate	Neg	Neg	None	13	Pos	Pos	Mild	No	No	40
6	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
8	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
11	Pos	Pos	Severe	Pos	Pos	None	15	.	.	.	No	No	.
14	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
16	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
19	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
20	Pos	Pos	Severe	Neg	Pos	None	14	.	.	.	No	No	36
29	Pos	Pos	Moderate	Neg	Neg	None	10	Neg	Neg	None	Yes	Yes	43
30	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
36	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	None	No	Yes	43
37	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Pos	None	No	Yes	42
39	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	36
42	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	37
44	Pos	Pos	Mild	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
45	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	40
47	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	Mild	Yes	No	40
50	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
51	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
60	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
63	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
64	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
66	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Pos	None	No	Yes	36
69	Pos	Pos	Severe	Neg	Pos	None	20	.	.	.	No	No	.
74	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
79	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
81	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	36

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368

All eligible enrolled patients, by treatment group

BASELINE

1ST REVISIT.

2ND REVISIT

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
83	Pos	Pos	Moderate	Neg	Neg	None	13	Neg	Neg	None	Yes	Yes	36
85	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
87	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	42
89	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	35
91	Pos	Pos	Moderate	Neg	Neg	None	11	Neg	Neg	None	Yes	Yes	39
93	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
96	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
97	Pos	Pos	Mild	Neg	Pos	None	15	.	.	None	No	No	.
98	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
102	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
104	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	43
105	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	43
110	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
119	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	43
122	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	38
124	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
126	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	37
127	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
129	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
130	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	35
133	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
134	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	35
137	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
138	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	38
142	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	43
144	Pos	Pos	Mild	Neg	Pos	None	15	Neg	Neg	None	Yes	Yes	38
145	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	No	No	.
147	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
											Yes	Yes	38

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368

All eligible enrolled patients, by treatment group

BASELINE

1ST REVISIT

2ND REVISIT

----- Treatment=Perrigo -----
 (continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
149	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	Mild	Yes	No	40
156	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
157	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Pos	None	No	Yes	38
158	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
161	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
163	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Neg	Mild	No	No	38
165	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	40
166	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
172	Pos	Pos	Moderate	Neg	Neg	None	13	Pos	Pos	None	No	Yes	41
173	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	46

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

APPEARS THIS WAY
ON ORIGINAL

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
(Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
Project Number 901368

All eligible enrolled patients, by treatment group

2ND REVISIT

1ST REVISIT

BASELINE

Treatment=Ortho

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
3	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
4	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
5	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
7	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
10	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
12	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
13	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	38
15	Pos	Pos	Moderate	Pos	Pos	None	15	Pos	Pos	None	NO	Yes	37
17	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
18	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
23	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
25	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
32	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	38
33	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	36
34	Pos	Pos	Mild	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	37
38	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	40
40	Pos	Pos	Moderate	Neg	Neg	None	12	Pos	Pos	Mild	NO	NO	40
41	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
43	Pos	Pos	Mild	Neg	Neg	None	14	Neg	Neg	Mild	Yes	No	36
46	Pos	Pos	Mild	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	37
40	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
52	Pos	Pos	Moderate	Pos	Pos	Moderate	20	Pos	Pos	None	NO	NO	36
53	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	30
59	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
61	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
62	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Pos	None	NO	Yes	36
65	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	NO	Yes	38
72	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Pos	None	NO	Yes	42

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368

All eligible enrolled patients, by treatment group

2ND REVISIT

1ST REVISIT

BASELINE

Treatment=Ortho
 (continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
75	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
76	Pos	Pos	Moderate	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	35
80	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
82	Pos	Pos	Moderate	Neg	Neg	None	13	Neg	Neg	None	Yes	Yes	34
84	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
88	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
92	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	36
94	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	34
95	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
99	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
100	Pos	Pos	Mild	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
111	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	35
112	Pos	Pos	Severe	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
121	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
123	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
128	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
132	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Pos	None	No	Yes	41
135	Pos	Pos	Mild	Pos	Neg	None	15				No	No	
136	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
139	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	41
140	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
141	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	41
143	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Pos	None	No	Yes	38
146	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Pos	None	No	Yes	41
148	Pos	Pos	Mild	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	37
150	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
159	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
160	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	40

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

2ND REVISIT

1ST REVISIT

----- Treatment=Ortho -----
 (continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
164	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
168	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
171	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	41
176	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	43

APPEARS THIS WAY
ON ORIGINAL

* Number of days post-treatment to review
 Source: formatted.sas Output: 14MAR96

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368

All ineligible patients, by treatment group

2ND REVISIT

1ST REVISIT

BASELINE

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
9	Pos	Pos	Severe	n/d	n/d	Moderate	6	.	.	.	No	No	.
21	Pos	Neg	Severe	Neg	Neg	Moderate	15	Pos	n/d	Moderate	No	No	36
22	Pos	Pos	Mild	Neg	Pos	None	20	.	.	.	No	No	42
27	Pos	Pos	Moderate	No	.
35	Pos	Pos	Severe	Neg	Neg	None	15	.	.	.	No	No	.
54	Pos	Pos	Moderate	Neg	Neg	None	17	.	.	.	No	No	.
55	Pos	Pos	Mild	No	.
68	Pos	Pos	Severe	Neg	Neg	None	15	.	.	.	No	No	.
70	Pos	Pos	Severe	Neg	Neg	Mild	15	.	.	.	No	No	.
73	Pos	Neg	Severe	No	.
78	Pos	Neg	Moderate	No	.
109	Pos	Neg	Mild	No	.
152	Pos	Pos	Moderate	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	50
154	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
170	Pos	Neg	Moderate	No	.
174	Pos	Pos	Moderate	No	.

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

APPEARS THIS WAY
ON ORIGINAL

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368

All ineligibile patients, by treatment group

2ND REVISIT

1ST REVISIT

Treatment=Ortho

BASELINE

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
24	Pos	Pos	Moderate	Pos	Pos	Mild	15	.	.	.	No	No	50
26	Pos	Neg	Moderate	No	.
31	Pos	Pos	Mild	No	.
49	Pos	Pos	Mild	Neg	Neg	Moderate	5	Neg	Neg	None	Yes	No	38
67	Pos	Pos	Severe	No	.
71	Pos	Neg	Severe	No	.
77	Pos	Pos	Severe	Neg	Neg	None	23	Neg	Pos	None	No	Yes	43
86	Pos	Neg	Moderate	No	.
90	Pos	Pos	Moderate	Neg	Neg	None	31	.	.	.	No	No	.
107	Pos	Neg	Mild	No	.
125	Pos	Neg	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
131	Pos	Neg	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
151	Pos	Pos	Moderate	Neg	Neg	Mild	21	Neg	Neg	None	Yes	Yes	57
153	Pos	Pos	Moderate	Pos	Pos	Mild	22	.	.	.	No	No	.
155	Pos	Neg	Moderate	No	.
169	Pos	Neg	Moderate	No	.
175	Pos	Neg	Moderate	No	.

* Number of days post-treatment to review

Source: Formated.sas Output: 14MAR96

APPEARS THIS WAY
ON ORIGINAL

Revised Table 2a

Mycological Cure Rate

Number of patients with mycological cure* (% of patients)		
<u>Perrigo</u>	<u>Ortho</u>	<u>90% C.I.</u>
49/66 (74.24%)	47/60 (78.33%)	-18.13% to 9.95%

* Mycological cure is defined as a negative KOH and Culture at both Visits 2 and 3.

Revised Table 2b

KOH and Culture Cure Rates at Visit 2 and Visit 3

Treatment Group	Number of patients with results negative (% of patients)			
	<u>Visit 2</u>		<u>Visit 3</u>	
	KOH	Culture	KOH	Culture
Perrigo	65/66 (98.48%)	61/66 (92.42%)	54/61 (88.52%)	50/61 (81.97%)
Ortho	57/60 (95.00%)	58/60 (96.67%)	55/58 (94.83%)	47/58 (81.03%)
Lower 90% C.I.	-3.35%	-12.41%	-16.23%	-12.47%
Upper 90% C.I.	10.32%	3.92%	3.62%	14.33%

APPEARS THIS WAY
ON ORIGINAL

Revised Table 3

Clinical Cure Rate

Number of patients with clinical cure*
(% of patients)

<u>Perrigo</u>	<u>Ortho</u>	<u>90% C.I.</u>
54/66 (81.82%)	55/60 (91.67%)	-21.21% to 1.51%

* Clinical cure is defined as an improvement (or absence) of symptoms at Visit 2 and absence of symptoms at Visit 3.

Revised Table 4

Overall Combined Mycological and Clinical Cure Rate

Number of patients with overall cure*
(% of patients)

<u>Perrigo</u>	<u>Ortho</u>	<u>90% C.I.</u>
47/66 (71.21%)	46/60 (76.67%)	-19.88% to 8.97%

* Overall cure is defined as both mycological cure and clinical cure.

APPEARS THIS WAY
ON ORIGINAL

DATE SUBMITTED: September 1, 1993
DATE RECEIVED: September 3, 1993
DATE OF AMENDMENT: November 16, 1994
DATE COMPLETED: December 5, 1995

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

Requested By: Division of Generic Drugs
HFD-630

Applicant: L. Perrigo Co.
117 Water Street
Allegan, Michigan 49010

Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Drug Category: Anti-fungal

Dose Form: Vaginal suppository

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

Purpose:

The purpose of this ANDA is to obtain market approval comparable to the innovator product of a generic form of miconazole 100mg vaginal insert manufactured by L. Perrigo Co. for the treatment of recurrent vaginal candidiasis.

The Applicant has conducted a study comparing the efficacy and safety of miconazole 100mg vaginal insert by Perrigo and Monistat-7 100mg vaginal insert (Ortho) in the treatment of women with Candida.

Background:

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

Study Design:

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

Monitoring: The study was conducted in accordance with the "Guidelines on Research Involving Human Subjects" (Medical Research Council of Canada, 1987). Regular monitoring visits were made to each study center during the study by _____

_____ Monitors who established that the protocol was being followed and that data were being collected accurately. At the conclusion of the study unused study medications were retained and stored with permanent study files by _____

_____ There was no mention in the data as to whether or not all evaluable patients took the full course of therapy. It can reasonably be concluded that they did, in the absence of data to the contrary based on the above monitoring.

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

ENTRY (BASELINE) VISIT:

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

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

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

- * Patients must not be expected to begin menses during the treatment period. KOH and culture were repeated if treatment start was delayed more than 7 days.
- * Sexually active patients must be using a reliable method of birth control (oral contraceptives, diaphragm with spermicide etc.)
- * Patients must agree to abstain from douches, tub baths, swimming, sexual intercourse and other activities likely to alter the disposition of drug in the vagina during treatment.
- * Sexual intercourse following the treatment period must involve the use of a condom.

* Clinical Determinations:

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

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

* Microbiological Determinations:

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

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

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

Exclusion Criteria:

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

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

Procedures

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

* Randomization Procedures:

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

* Drug Administration:

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

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

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

* Patient Instructions:

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

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

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

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

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

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

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

Evaluation of Efficacy Outcome

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

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

FIRST POST-TREATMENT VISIT:

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

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

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

Clinical Efficacy and Mycological Efficacy:

CLINICAL OUTCOME:

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

MYCOLOGICAL OUTCOME:

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

SECOND POST-TREATMENT VISIT:

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

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

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

CLINICAL OUTCOME:

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

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

MYCOLOGICAL OUTCOME:

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

THERAPEUTIC OUTCOME:

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

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

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

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

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

**APPEARS THIS WAY
ON ORIGINAL**

RESULTS:

A total of nine investigators (6 gynecologists and 3 general practitioners) enrolled a total of 159 patients of whom 82 were randomized to the Perrigo 100mg vaginal insert and 77 were randomized to the Ortho Monistat-7 100mg insert. They were responsible to the _____ or the recruitment of patients to participate in the studies that were conducted for this ANDA. The curriculum vitae of each of the investigators was carefully reviewed and each was found to be qualified to conduct the study. The investigator, the geographical location of the investigator, and the number of patients enrolled for each investigator are listed in Table 1 below.

Table 1

Patient Enrollment By Investigator

Investigator/Location	Patients Given Miconazole (Perrigo)	Patients Given Monistat-7	Total
_____	14	14	28
_____	14	14	28
_____	14	14	28
_____	14	12	26
_____	12	12	24
_____	9	8	17
_____	2	2	4
_____	3	0	3
_____	0	1	1
<u>TOTAL</u>	82	77	159

Study Population:

A total of 159 patients was recruited for the study, as shown in Table 1, of which 130 were eligible for analysis and evaluable. Eligibility criteria included:

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

There were 82 patients in the Perrigo arm of the study and 77 in the Ortho group. 14 Perrigo and 15 Ortho patients were excluded as ineligible for efficacy analysis (Table 2). 68 patients remained in the Perrigo group and 62 patients in the Ortho group.

Table 2

**Exclusion From Efficacy Analysis
By Applicant Perrigo N = 29**

Reason	Perrigo	Ortho
Negative culture on admission	5	9
Protocol violation (wrong laboratory, menses during treatment, etc.)	0	1
Lost to follow-up or missing data:		
Came for Visit 1 only	3	2
Came for Visit 1 and 2 only	4	0
Drop out from ADR	1	0
Came too late for Visit 2 or 3	1	3
Total	14	15

Table 3

Ineligible For Efficacy Analysis N = 29

Investigator	Patient Number	Perrigo/Ortho	Reason
1. ✓	# 09	Perrigo	5
2. ✓	# 21	Perrigo	3c
3. ✓	# 26	Ortho	3c
4. ✓	# 27	Perrigo	2a
5. ✓	# 31	Ortho	2a
6. ✓	# 35	Perrigo	2b
7. ✓	# 49	Ortho	3a
8. ✓	# 54	Perrigo	2b
9. ✓	# 55	Perrigo	2a
10. ✓	# 67	Ortho	2a
11. ✓	# 68	Perrigo	2b
12. ✓	# 70	Perrigo	2b
13. ✓	# 71	Ortho	3c
14. ✓	# 73	Perrigo	3c
15. ✓	# 77	Ortho	2d
16. ✓	# 78	Perrigo	3c
17. ✓	# 86	Ortho	3c
18. ✓	# 90	Ortho	2d
19. ✓	# 107	Ortho	3c
20. ✓	# 109	Perrigo	3c
21. ✓	# 125	Ortho	3c
22. ✓	# 131	Ortho	3c
23. ✓	# 153	Ortho	2d
24. ✓	# 154	Perrigo	2d
25. ✓	# 155	Ortho	3c
26. ✓	# 169	Ortho	3c
27. ✓	# 170	Ortho	3c
28. ✓	# 174	Perrigo	2a
29. ✓	# 175	Ortho	3c

CODE:

- 2a - Patient came for visit 1 only (5 patients)
- 2b - Patient came for visit 1 & 2 only (4 patients)
- 2d - Came too early/late for visit 2 or 3 (4 patients)
- 3a - Protocol violation (inclusion/exclusion) (1 patient)
- 3c - Negative KOH/culture at visit 1 (14 patients)
- 5 - Drop out for adverse drug reaction (1 patient)

Table 4
Exclusion From Efficacy Analysis
Per Investigator

<u>Investigator</u> (# enrolled in parenthesis)	Patients Given Miconazole (Perrigo)	Patients Given Monistat-7 (Ortho)	Total
(1)	0	0	0
(3)	2	0	2
(17)	3	1	4
(4)	1	1	2
(28)	4	5	9
(24)	3	5	8
(28)	1	0	1
(28)	0	2	2
(26)	0	1	1
(159)	14	15	29

Investigators: Nine investigators (6 gynecologists and three general practitioners) from various locations in Canada recruited patients who were evaluable for efficacy analysis. The investigators, their geographical location and the number of evaluable patients for each are listed in Table 5 below:

Table 5
Patients Evaluable by Applicant Perrigo
For 1st and 2nd re-visits

INVESTIGATOR/LOCATION	PATIENTS GIVEN MICONAZOLE (PERRIGO)	PATIENTS GIVEN MONISTAT-7 (ORTHO)	TOTAL
(OB-GYN)	10	9	19
(OB-GYN)	14	12	26
(OB-GYN)	13	14	27
(OB-GYN)	14	11	25
(OB-GYN)	9	7	16
(G.P.)	6	7	13
(G.P.)	1	1	2
OB-GYN)	1	0	1
(G.P.)	0	1	1
Total	68	62	130

Table 6
Demographic DATA

Observed	Minimum-Maximum	Mean
Perrigo N = 68	Ht (cm) 152-183 (60-72")	163 (65")
	Wt (kg) 45-109 (99-238#)	61 (132#)
	Age (yr) 16-63 (16-63 yr)	31 (31yr)
Ortho N = 62	Ht (cm) 140-180 (55-71")	161 (63")
	Wt (kg) 45-86 (99-189#)	60 (132#)
	Age (yr) 15-65 (15-65 yr)	32 (32yr)

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

The patients were not classified by race.

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ON ORIGINAL

CLINICAL OUTCOME - PER APPLICANT

Table 7

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
Perrigo	62/68 (91%)	50/63 (79%)
Ortho	58/62 (93%)	48/60 (80%)

Table 7a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
Perrigo	68/68 (100%)	55/64 (86%)
Ortho	61/62 (98%)	56/60 (93%)

Table 7b

Therapeutic Cure Rate

Treatment Group	Visit 3
Perrigo	48/68 (70%)
Ortho	47/62 (75%)

Note: The denominator values in Tables 7 & 7a at visit 3 differ from visit 2. Seven (7) patients were not evaluated for mycological response because they did not return for visit 3. They were patients # 11,20,69,97,& 144 (Perrigo) and 52 & 135 (Ortho). Patient # 20, a mycological failure at visit 2, did return for clinical evaluation at visit 3. The total number of patients not evaluated for clinical response was six (6)-- patients # 11,69,97 & 144 (Perrigo) and 52 and 135 (Ortho).

CLINICAL OUTCOME - PER MEDICAL OFFICER

Table 8

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
Perrigo	51/56 (91%)	40/56 (71%)
Ortho	52/55 (95%)	44/55 (80%)

Table 8a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
Perrigo	55/56 (98%)	47/56 (86%)
Ortho	54/55 (98%)	50/55 (91%)

Table 8b

Therapeutic Cure Rate

Treatment Group	Visit 3
Perrigo	40/56 (71%)
Ortho	43/55 (78%)

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

Clinical Outcome Summary:

At visit 2, the Applicant demonstrated a 91% mycological cure rate for the Perrigo product and a 93% cure rate for the Ortho product. The Medical Officer found comparable cure rates at visit 2 of 91% for the Perrigo product and 95% for the Ortho product. At visit 3, the Applicant demonstrated a 79% mycological cure rate for the Perrigo product versus 80% for the Ortho product. The Medical Officer showed a 71% mycological cure rate at visit 3 for the Perrigo product and an 80% cure rate for the Ortho product.

The clinical cure rates at visit 2 per the Applicant were 100% (Perrigo) and 98% (Ortho). The Medical Officer found clinical cure rates at visit 2 of 98% (Perrigo) and 98% (Ortho). At visit 3, the Applicant showed an 86% clinical cure rate for the Perrigo product and a 93% cure rate for the Ortho product. The Medical Officer showed an 86% clinical cure rate at visit 3 for the Perrigo product and a 91% cure rate for the Ortho product.

The therapeutic cure rates were 70% for the Perrigo group of patients and 75% for those given the Ortho product, per the Applicant. The Medical Officer's review demonstrated therapeutic cure rates of 71% for the Perrigo group and 78% for the Ortho group of patients.

SAFETY ANALYSIS:

Two patients reported one adverse event each. None of the reported events was unusual or considered to be serious.

Table 9

Adverse Events			
Treatment Group	Description	Reported at Visit	Related to Medication?
Perrigo pt. #9	Redness, swelling edema of vulva, acute burning Withdrew from study	2	Yes
Ortho pt. #112	Itching	2	Uncertain

RECOMMENDATION:

From a clinical standpoint, I do not recommend approval of L. Perrigo Co.'s Miconazole Nitrate Vaginal Suppository, 100 mg for the treatment of recurring vulvovaginal candidiasis.

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

APPEARS THIS WAY
ON ORIGINAL

C, 1st ... D.

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

Concurrence Only:
HFD/520/Dir/MFanning
HFD/520/SMO/RAlbrecht

12/18/95
12/12/95

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 1.

2. ANDA 74-395

3. NAME AND ADDRESS OF APPLICANT

L. Perrigo Co.
117 Water Street
Allegan MI 49010

4. LEGAL BASIS FOR SUBMISSION

The applicants claim for submission of this ANDA is supported by the absence of any patent certification and exclusivity statements as referenced in the listings found in the 13th edition of the approved drug products (Orange Book).

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

Miconazole Nitrate

7. NONPROPRIETARY NAME

Miconazole Nitrate

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

N/A

9. AMENDMENTS AND OTHER DATES:

July 30, 1993-----Application date

10. PHARMACOLOGICAL CATEGORY

Antifungal

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

DMF _____
DMF- _____

13. DOSAGE FORM

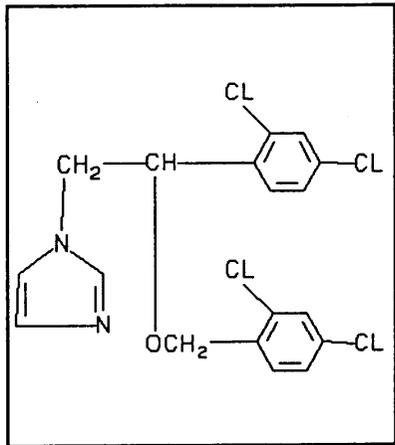
Suppository

14. POTENCY

100 mg

15. CHEMICAL NAME AND STRUCTURE

1-[2,4-dichloro-β-[(2,4 dichlorobenzyl) oxy] phenethyl] imidazole mononitrate



16. RECORDS AND REPORTS

N/A

17. COMMENTS

A large, empty rectangular box with a dashed horizontal line across its middle, intended for handwritten comments.

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18. CONCLUSIONS AND RECOMMENDATIONS

Not approved

19. REVIEWER:

Lamont M. Fulton

Endorsed by P.Schwartz, Ph.D.

DATE COMPLETED:

12-3-93

02-01-94

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1. CHEMISTRY REVIEW NO 2.

2. ANDA 74-395

3. NAME AND ADDRESS OF APPLICANT

L. Perrigo Co.
117 Water Street
Allegan MI 49010

4. LEGAL BASIS FOR SUBMISSION

The applicants claim for submission of this ANDA is supported by the absence of any patent certification and exclusivity statements as referenced in the listings found in the 13th edition of the approved drug products (Orange Book).

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

Miconazole Nitrate

7. NONPROPRIETARY NAME

Miconazole Nitrate

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

N/A

9. AMENDMENTS AND OTHER DATES:

July 30, 1993-----Application date
February 16, 1994-----Deficiency Ltr.
March 8, 1994-----Amendment Ltr.

10. PHARMACOLOGICAL CATEGORY

Antifungal

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

DMF

DMF-

13. DOSAGE FORM

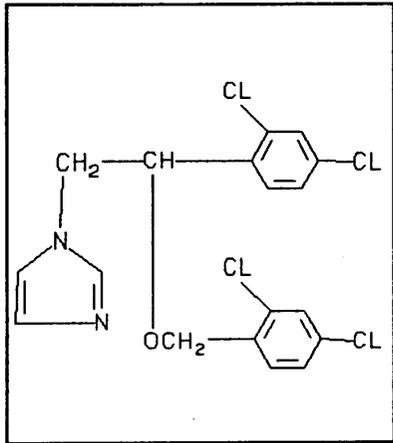
Suppository

14. POTENCY

100 mg

15. CHEMICAL NAME AND STRUCTURE

1-[2,4-dichloro-β-[(2,4 dichlorobenzyl) oxy] phenethyl] imidazole mononitrate

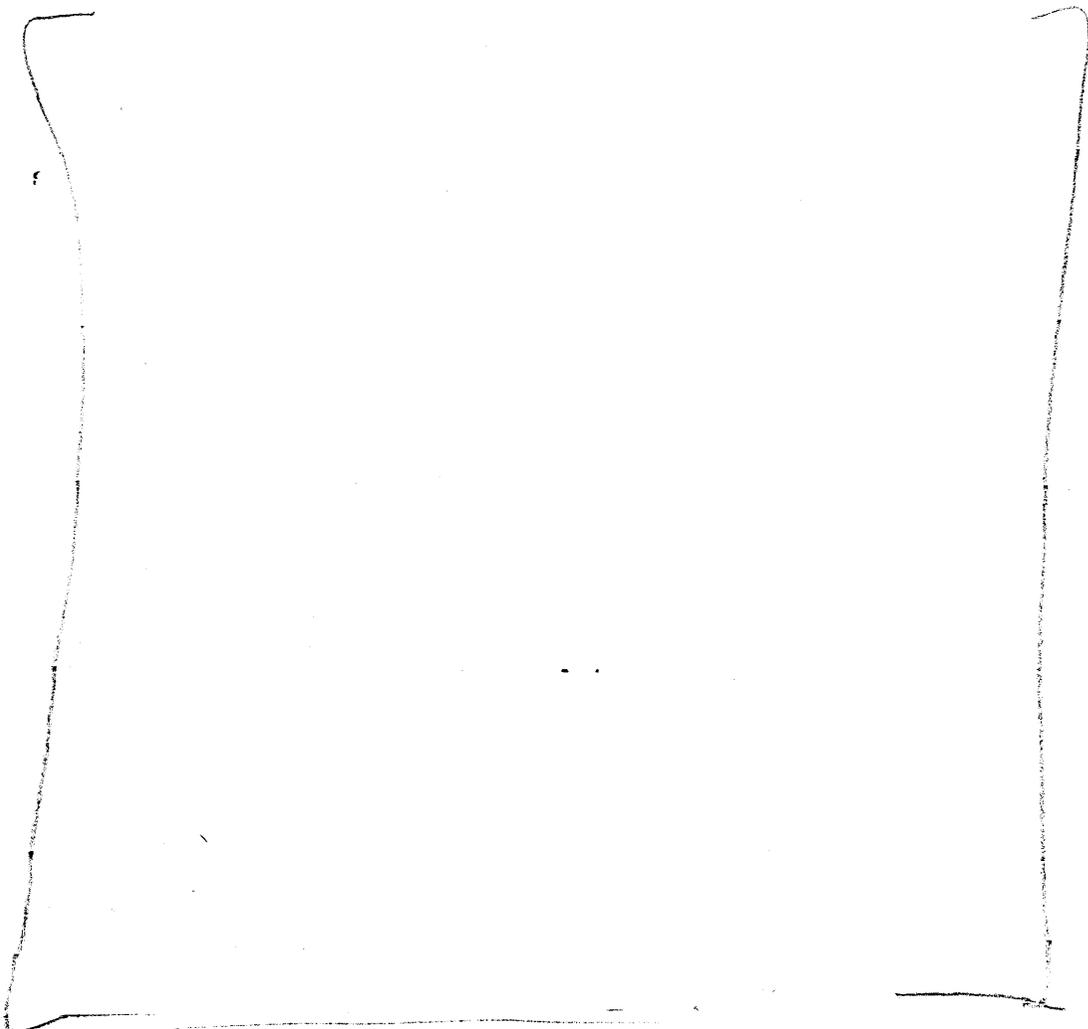


16. RECORDS AND REPORTS

N/A

17. COMMENTS





18. CONCLUSIONS AND RECOMMENDATIONS

Not approved

19. REVIEWER:

DATE COMPLETED:

Lamont M. Fulton

10-11-94

Endorsed by P.Schwartz, Ph.D.

10-11-94

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1. CHEMIST'S REVIEW NO. 3
 2. ANDA: 74-395
 3. NAME AND ADDRESS OF APPLICANT:

L. Perrigo Co.
117 Water Street
Allegan, MI 49010
 4. LEGAL BASIS for ANDA SUBMISSION: **Satisfactory.**

See CR #2 by L. Fulton, dated 10/11/94.
 5. SUPPLEMENT(s): N/A
 6. PROPRIETARY NAME: Miconazole Nitrate
 7. NONPROPRIETARY NAME: Miconazole Nitrate
 8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
 9. AMENDMENTS AND OTHER DATES:

Original Submission: 7/30/93
Deficiency Letter #1: 2/16/94
Amendment Letter: 3/8/94
Deficiency Letter #2: 10/28/94
Amendment Letter: 11/15/94
Amendment Letter: 12/15/94
 10. PHARMACOLOGICAL CATEGORY: *Antifungal*
 11. Rx or OTC: OTC
- CONCLUSIONS AND RECOMMENDATIONS: **NOT APPROVABLE**

REVIEWER:

DATE COMPLETED:

Daniel S. James, Ph.D.

11/3/95

Endorsed by P. Schwartz, Ph.D.

11/3/95

12. RELATED IND/NDA/DMF(s):

See CR #2 by L. Fulton, dated 10/11/94.

DMF
DMF
DMF

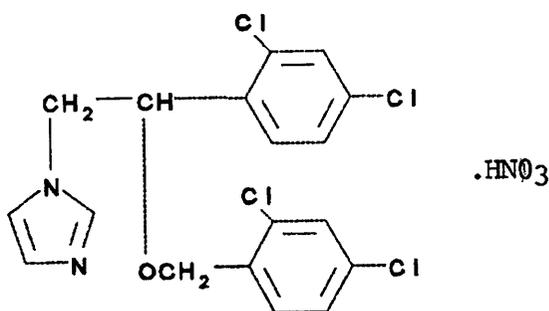
13. DOSAGE FORM:

Suppository

14. POTENCY:

100 mg

15. CHEMICAL NAME AND STRUCTURE: 1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]imidazole mononitrate.



Mol. Form.: C₁₈H₁₄Cl₄N₂O.HNO₃
Mol. Wt.: 479.15
M.P.: 170.5°C (M.I.)
CAS: 22832-87-7

16. RECORDS AND REPORTS: N/A

17. COMMENTS: This ANDA is deficient for the following reasons:

1. Holders of DMF # _____ and DMF #'s _____ have been notified of deficiencies in their Drug Master Files. Applicant will be requested not to respond to this communication until receipt of notice from the DMF holders that they have responded to our communication to them.
2. Labeling is not satisfactory and must be revised.
3. GMP inspection requirements are pending.
4. Bioequivalency status is under review.

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1. CHEMIST'S REVIEW NO. 4

2. ANDA: 74-395

3. NAME AND ADDRESS OF APPLICANT:

L. Perrigo Co.
117 Water Street
Allegan, MI 49010

4. LEGAL BASIS for ANDA SUBMISSION:

See CR #2 by L. Fulton, dated 10/11/94

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: Miconazole Nitrate

7. NONPROPRIETARY NAME: Miconazole Nitrate

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

9. AMENDMENTS AND OTHER DATES:

Original Submission:	7/30/93
Deficiency Letter #1:	2/16/94
Amendment Letter:	3/8/94
Deficiency Letter #2:	10/28/94
Amendment Letter:	11/15/94
Amendment Letter:	12/15/94
Deficiency Letter #3:	11/14/95
Amendment Letter:	12/14/95

10. PHARMACOLOGICAL CATEGORY: *Antifungal*

11. Rx or OTC: OTC

CONCLUSIONS AND RECOMMENDATIONS: NOT APPROVABLE

<u>REVIEWER:</u>	<u>DATE COMPLETED:</u>
Daniel S. James, Ph.D.	3/27/96
Endorsed by P. Schwartz, Ph.D.	4/1/96

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15. CHEMICAL NAME AND STRUCTURE

C₁₈H₁₄Cl₄N₂O•HNO₃. 479.15. 1*H*-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate. 22832-87-7. USP 23, page 1026.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is Approvable

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D.

3/3/97

cc: ANDA 74-395
Division File
Field Copy

Endorsements:

/s/ 3/3/97
HFD-627/NNashed
HFD-627/PSchwartz */s/* 3/3/97
X:\NEWFIRMS\NZ\PERRIGO\LTRS&REV\74-395.5
F/t by: gp/3/3/97

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
(Consult)

ANDA#: 74-395 AUG 1 1996

Applicant: L. Perrigo Co.

Name of Drug: Miconazole Nitrate Vaginal Suppository, 100mg

Documents Reviewed: Medical Officer's Data Set

Indication: Vaginal Candidiasis

Medical Input: Dr. Andrea Meyerhoff, HFD-520

A. INTRODUCTION

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

2-1
Generic Drug Division trials of vaginal care products are generally standardized, therefore, a full statistical evaluation of the total submission is only done if problems in conduct or reporting of trial results are noted by the Reviewing Medical Officer (RMO). When there are no problems, our review is confined to check statistical results developed by the RMO or to compute confidence intervals on data as derived by the RMO. Since clinical trial data is not provided to the statistician, no evaluation of consistency among (between) investigators by treatment can be made. If the odds ratios differ significantly among the investigators, the following evaluation will not account for this.

B. CALCULATIONS AND EVALUATION

All calculations are based on the RMO's data as supplied on July 30, 1996. All confidence interval results are presented as two-sided 90% confidence intervals in the format $_{nt, nc} (CI)_{pt, pc}$, where n_t and p_t are respectively the sample size and success rates for the test agent (Perrigo's product - miconazole insert 100 mg) and n_c and p_c are similarly defined for the control agent (Ortho's product - Monistat-7 miconazole insert 100 mg).

Mycological and clinical response rates are secondary efficacy criteria and the therapeutic response rate is the primary efficacy criterion.

The following CIs are based on the Medical officer's data. For clinical response at the first post-treatment visit (V2), the cure rates for the Perrigo and Ortho products are all 100%, the 90% CIs do meet the Generic Drug equivalency criteria of ± 0.20 . At second post-treatment visit (V3) the Perrigo versus Ortho 90% CI is $_{58,52}(-.21, .153)_{.85, .94}$. For mycological response at the first post-treatment visit (V2), the Perrigo versus Ortho 90% CI is $_{58,52}(-.119, .579)_{.93, .96}$. At second post-treatment visit (V3) the Perrigo versus Ortho 90% CI is $_{58,52}(-.16, .135)_{.78, .79}$.

For therapeutic response at second post-treatment visit (V3), the Perrigo versus Ortho 90% CI is $_{58,52}(-.199, .109)_{.72, .77}$.

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

Except the clinical cure rates at second post-treatment (V3), all of the 90% CIs for the secondary efficacy variables of mycological and clinical cure rates do meet the Generic Drug equivalency criteria of ± 0.20 . For the primary efficacy response, the 90% CIs for the therapeutical cure rates also meet the Generic Drug equivalency criteria of ± 0.20 .

151

8/1/96

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

cc:

Orig. ANDA 74-395

HFD-520

HFD-520/Dr. Feigal

HFD-520/Dr. Leissa

HFD-520/Dr. Meyerhoff

HFD-520/Dr. Chi

✓ HFD-630/Ms. Parise

HFD-725/Dr. Harkins

HFD-725/Dr. Lin

HFD-344/Dr. Thomas

Chron.

This review contains 2 pages.

**APPEARS THIS WAY
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Statistical Review and Evaluation
(CONSULT)

NOV 30 1995

ANDA#: 74-395

Applicant: L. Perrigo Co.

Name of Drug: Miconazole Nitrate Vaginal Suppository, 100 mg

Documents Reviewed: Medical Officer's Review Submitted for Consult 12/27/95

Drug Category: Anti Fungal

Indication: Recurrent Vaginal Candidiasis.

Review Type: Clinical

Medical Input: Dr. Julius Piver, HFD-520

A. INTRODUCTION

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

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

B. Calculations and Evaluation

All calculations are based on data as supplied by the RMO. No effort has been made to check for internal consistency or to make other data validity checks. All confidence interval results are presented as two-sided 90% confidence intervals in the format

$(CI)_{pt, pc}$ where n_t and p_t are respectively the sample size and success rates for the test

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

The sponsor's visit 2 data, comparing Perrigo (the sponsor's product) to Ortho yield the following 90% CI for Mycological cure rates: $_{68.62} (-.11,.07)_{.91,.93}$ whereas the same CI using the RMOs data is $_{56.55} (-.13,.06)_{.91,.95}$. Each show Perrigo's product to be statistically equivalent to the Ortho product.

The sponsor's visit 3 data, comparing Perrigo (the sponsor's product) to Ortho yield the following 90% CI for Mycological cure rates: $_{63.60} (-.14,.12)_{.79,.80}$ whereas the same CI using the RMOs data is $_{56.55} (-.23,.06)_{.71,.80}$. The sponsor's data show the Perrigo product to be statistically equivalent to the Ortho product whereas the RMOs data shows inequivalency with possible inferiority.

The sponsor's visit 2 data, comparing Perrigo (the sponsor's product) to Ortho yield the following 90% CI for Clinical cure rates: $_{68.62} (-.02,.05)_{.100,.98}$ whereas the same CI using the RMOs data is $_{56.55} (-.06,.06)_{.98,.98}$. Each show the products to be statistically equivalent.

The sponsor's visit 3 data, comparing Perrigo (the sponsor's product) to Ortho yield the following 90% CI for Clinical cure rates: $_{64.60} (-.18,.02)_{.86,.93}$ whereas the same CI using the RMOs data is $_{56.55} (-.18,.07)_{.86,.91}$. Both show the products to be statistically equivalent.

The sponsor's visit 3 data, comparing Perrigo (the sponsor's product) to Ortho yield the following 90% CI for the primary efficacy variable, Therapeutic cure rates: $_{68.62} (-.19,.09)_{.70,.75}$ whereas the same CI using the RMOs data is $_{56.55} (-.22,.09)_{.71,.78}$. The sponsor's data indicate the two products are statistically equivalent, however the RMO's data show the Perrigo product is not therapeutically equivalent to the Ortho product.

REVIEWER'S COMMENT: Based on the RMO's data base for the primary efficacy endpoint, i.e., therapeutic cure rates, these analyses show Perrigo's Miconazole Nitrate Suppository, 100 mg to be inequivalent to the Ortho Pharmaceutical Corporation's formulation.

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

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

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-395 SPONSOR: L. Perrigo Co..

DRUG AND DOSAGE FORM: Miconazole Nitrate Vaginal Suppository

STRENGTHS(s): 100 mg

TYPE OF STUDY: Comparative Clinical Study

STUDY SITE: _____

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

L. Perrigo and Ortho's, miconazole nitrate vaginal suppositories are qualitatively and quantitatively similar.

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

DISSOLUTION: Not required.

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

INITIAL: IS/ **DATE** 3/5/97

BRANCH CHIEF: Shrinivas. G. Nerurkar, Ph.D. **BRANCH:** II

INITIAL: IS/ **DATE** 3/6/1997

for **DIRECTOR**

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

INITIAL: IS/ **DATE** 3/6/97

DIRECTOR

OFFICE OF GENERIC DRUGS:

INITIAL: IS/ **DATE** 3/11/97

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

BASELINE

1ST REVISIT

2ND REVISIT

-----Treatment-Perrigo-----

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
1	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	39
2	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	42
6	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
8	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
11	Pos	Pos	Severe	Pos	Pos	None	15	.	.	.	No	No	.
14	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
16	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
19	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	39
20	Pos	Pos	Severe	Neg	Pos	None	14	.	.	.	No	No	.
X 22	Pos	Pos	Mild	Neg	Pos	None	28	.	.	.	No	No	42
29	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	43
30	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
36	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	None	No	Yes	43
37	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Pos	None	No	Yes	42
39	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	36
X 44	Pos	Pos	Moderate	Neg	Neg	Mild	23	Neg	Neg	None	Yes	Yes	45
X 45	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
X 47	Pos	Pos	Moderate	Neg	Neg	Mild	22	Neg	Neg	Mild	Yes	Yes	47
50	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
51	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
60	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
63	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
64	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
66	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	No	Yes	44
69	Pos	Pos	Severe	Neg	Pos	None	20	Neg	Pos	None	No	Yes	36
74	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
79	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
81	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	35
83	Pos	Pos	Moderate	Neg	Neg	None	13	Neg	Neg	None	Yes	Yes	35
85	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37

* Number of days post-treatment to review

(4)

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

BASELINE

1ST REVISIT

2ND REVISIT

Treatment-Perrigo
(continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
87	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	42
89	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	35
91	Pos	Pos	Moderate	Neg	Neg	None	11	Neg	Neg	None	Yes	Yes	39
93	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
96	Pos	Pos	Severe	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	43
97	Pos	Pos	Mild	Neg	Pos	None	21				MO	MO	
98	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
102	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
104	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	43
105	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	MO	MO	43
110	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
119	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	43
X122	Pos	Pos	Moderate	Neg	Neg	None	24	Neg	Neg	None	Yes	Yes	45
124	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
126	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
127	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
X129	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	45
130	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	38
133	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
X134	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	48
137	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
X138	Pos	Pos	Mild	Neg	Neg	None	27	Neg	Neg	None	Yes	Yes	49
142	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
144	Pos	Pos	Mild	Neg	Pos	None	20				MO	MO	
145	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
147	Pos	Pos	Mild	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	42
149	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	Mild	Yes	MO	40
X152	Pos	Pos	Moderate	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	50
156	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
157	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Pos	None	MO	Yes	43

* Number of days post-treatment to review

5

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

BASILINE

1ST REVISIT

2ND REVISIT

Treatment-Perrigo
 (continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
X 158	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	45
161	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Pos	None	No	Yes	43
X 163	Pos	Pos	Moderate	Neg	Neg	None	22	Pos	Neg	Mild	No	No	45
X 165	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	47
166	Pos	Pos	Moderate	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
172	Pos	Pos	Moderate	Neg	Neg	None	13	Pos	Pos	None	No	Yes	41
173	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	45

(3)

APPEARS THIS WAY
 ON ORIGINAL

* Number of days post-treatment to review

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

BASELINE

1ST REVISIT

2ND REVISIT

Treatment-Ortho
(continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
80	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
82	Pos	Pos	Moderate	Neg	Neg	None	13	Neg	Neg	None	Yes	Yes	34
84	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
88	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
92	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	36
94	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	34
95	Pos	Pos	Mild	Neg	Neg	None	23	Neg	Pos	None	No	Yes	44
99	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
100	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
111	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	35
X 112	Pos	Pos	Severe	Neg	Neg	None	25	Neg	Neg	None	Yes	Yes	48 X
121	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
121	Pos	Pos	Moderate	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	43
128	Pos	Pos	Mild	Neg	Neg	None	18	Neg	Neg	None	No	Yes	41
132	Pos	Pos	Mild	Neg	Neg	None	18	Neg	Pos	None	No	Yes	44
135	Pos	Pos	Mild	Pos	Neg	None	21	Neg	Neg	None	No	No	43
136	Pos	Pos	Moderate	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	43
139	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
140	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
X 141	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	46 X
143	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Pos	None	No	Yes	43
146	Pos	Pos	Moderate	Neg	Neg	None	19	Neg	Pos	None	No	Yes	45
148	Pos	Pos	Mild	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	39
150	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
X 151	Pos	Pos	Moderate	Neg	Neg	Mild	21	Neg	Neg	None	Yes	Yes	57 X
159	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
X 160	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	47 X
X 164	Pos	Pos	Mild	Neg	Neg	None	23	Neg	Neg	None	Yes	Yes	45 X
X 168	Pos	Pos	Mild	Neg	Neg	None	23	Neg	Neg	None	Yes	Yes	44 X
171	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	41

* Number of days post-treatment to review

(5)

Comparison of Micromazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

BASLINE

1ST REVISIT

2ND REVISIT

Treatment-Ortho

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
3	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
4	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
5	Pos	Pos	Severe	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	37
7	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	42
10	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
12	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
13	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
15	Pos	Pos	Moderate	Pos	Pos	None	17	Neg	Neg	None	Yes	Yes	38
17	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	No	Yes	37
18	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
23	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
X 24	Pos	Pos	Moderate	Pos	Pos	Mild	15	Neg	Neg	None	Yes	Yes	43
25	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	No	No	50 X
32	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	43
33	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	38
34	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
38	Pos	Pos	Mild	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	37
40	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	42
41	Pos	Pos	Mild	Neg	Neg	None	12	Pos	Pos	Mild	No	No	40
43	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
46	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	Mild	Yes	No	44
48	Pos	Pos	Mild	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	37
54	Pos	Pos	Moderate	Pos	Pos	Moderate	22	Neg	Neg	None	Yes	Yes	44
53	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	No	No	44
59	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
61	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
62	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
65	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	No	Yes	39
72	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	No	Yes	43
75	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	No	Yes	42
76	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43

* Number of days post-treatment to review

10

1

FEB 3 1997

ANDA # 74-395
Miconazole Nitrate Vaginal Suppositories, 100 mg
Reviewer: S. P. Shrivastava
WP # 74395S.396

L. Perrigo Co.
Allegan, MI
Submission Date:
March 21, 1996

REVIEW OF A BIOEQUIVALENCE STUDY

The firm has resubmitted the comparative clinical study for its OTC drug product miconazole nitrate vaginal suppositories, 100 mg, which was initially reviewed and found unacceptable (see review by S.P. Shrivastava, 1/31/96) by the Division of Anti-Infective Drug Products (HFD-520). Current review includes corrections in programming error in summary table previously submitted. The consultants' reviews are attached (Attachments 1-3). Comparative composition of the formulations are given in Table 1.

COMMENTS

1. The firm should develop dissolution methods and specifications, submit the data to the agency at the earliest, and use them as quality control tool.
2. There are three evaluable parameters considered by the Medical Officer at FDA: clinical cure rate, mycological cure rate, and therapeutic cure rate. The medical and statistical evaluations indicate, that on the third visit, mycologic, clinical and therapeutic cure rates for Perrigo and Ortho miconazole nitrate vaginal suppositories are equivalent. The parameter values were obtained at second (V2) and third (V3) visits, and were statistically analyzed using 90% CI criteria.
3. The inactive ingredients in L. Perrigo Co., miconazole nitrate vaginal suppository, 100 mg and Monistat-7^R (Ortho), 100 mg, are qualitatively and quantitatively similar. The lot size was  dosage units.

RECOMMENDATION

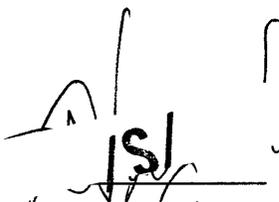
The comparative clinical study conducted by L. Perrigo Co., on its miconazole nitrate vaginal suppositories, 100 mg, Lot # 2T6450, comparing it to Ortho's Monistat-7, 100 mg, Lot #22A125 has been found acceptable by the Division of Anti-Infective Drug Products, and by the Division of Bioequivalence. The study demonstrates that L. Perrigo's miconazole nitrate vaginal suppositories, 100 mg, are bioequivalent to the reference product, Monistat-7^R, 100 mg, manufactured by Ortho.

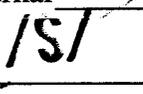
The firm should be informed of the comment #1 and recommendation.

/S/

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

RD INITIALED S Nerurkar
FT INITIALED S Nerurkar

 /S/ Date 1/24/1997

Concur:  /S/ Date: 2/3/97

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Attachment-3

SPS/sps/12-30-96/74395S.396

cc: ANDA #74-395 (Original, Duplicate), HFD-655 (S Nerurkar, S Shrivastava), Drug File,
Div. File

APPEARS THIS WAY
ON ORIGINAL

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

Table 1. Comparative Formulation

<u>Ingredients</u>	<u>L. Perrigo</u> mg/Suppository	<u>Ortho USA</u> mg/Suppository
Miconazole nitrate, USP	100	100
Hydrogenated Vegetable Oil	<u> </u>	N/A

APPEARS THIS WAY
ON ORIGINAL

JAN 31 1996

ANDA # 74-395
Miconazole Nitrate Vaginal Suppositories, 100 mg
Reviewer: S. P. Shrivastava
WP # 74395S.793

L. Perrigo Co.
Allegan, MI
Submission Date:
7/30/93; 12/15/94

Review of a Bioequivalence Study

The firm has submitted a comparative clinical study for its miconazole nitrate vaginal suppositories, 100 mg, which was sent for consult to the Division of Anti-Infective Drug Products (HFD-520), and to the Biometrics Division (HFD-725). The consults' reviews are attached (Attach. 1, 2). Comparative composition of the formulations are given in Table 1.

Comments

1. The generic vaginal suppositories must meet the 90% confidence interval for determining the therapeutic cure rates (mycological and ~~clinical~~), with a $\pm 20\%$ delta value. The medical and statistical evaluations indicate, that on the third visit, mycologic cure rates for Perrigo and Ortho miconazole nitrate vaginal suppositories are inequivalent, the clinical cure rates are equivalent, and the therapeutic cure rates are also inequivalent. Therefore, L. Perrigo's miconazole nitrate vaginal suppository is not bioequivalent to the Ortho's Monistat-7^R (Re: Attachment 1, p-18).
2. Summary report, IRB approval letter, drug composition, and product formulation data did not document the product Lot # used in the study. Lot # 2T6450 for test and Lot #22A125 for Ortho product was recorded only in the protocol. In future, the firm should document the Lot # of the products adequately.
3. The inactive ingredients in L. Perrigo Co., miconazole nitrate vaginal suppository, 100 mg and Monistat-7^R (Ortho), 100 mg, are qualitatively and quantitatively similar. The lot size was — , dosage units.

Recommendation

The comparative clinical study conducted by L. Perrigo Co., on its miconazole nitrate vaginal suppositories, 100 mg, Lot # 2T6450, comparing it to Ortho's Monistat-7, 100 mg, Lot #22A125 has been found unacceptable by the Division of Anti-Infective Drug Products, and by the Division of Bioequivalence. The study demonstrates that L. Perrigo's miconazole nitrate vaginal suppositories, 100 mg, are not bioequivalent to the reference product, Monistat-7^R, 100 mg, manufactured by Ortho.

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


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

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

Table 1. Comparative Formulation

<u>Ingredients</u>	<u>L. Perrigo</u> mg/Suppository	<u>Ortho USA</u> mg/Suppository
Miconazole nitrate, USP	100	100
Hydrogenated Vegetable Oil	—	N/A

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

ADMINISTRATIVE DOCUMENTS

CDER Establishment Evaluation Report
for March 14, 1997

Application: **ANDA 74395/000**
Stamp: **04-AUG-1993** Regulatory Due:
Applicant: **L PERRIGO**
117 WATER ST
ALLEGAN, MI 49010

Priority:
Action Goal:
Brand Name:
Established Name: **MICONAZOLE NITRATE**
Generic Name:
Dosage Form: **SUP (SUPPOSITORY)**
Strength: **100 MG VAGINAL**

Org Code: **600**

District Goal: **04-OCT-1994**

FDA Contacts: **J. BUCCINE (HFD-617) 301-594-1841 , Project Manager**
D. JAMES (HFD-629) 301-594-1841 , Review Chemist
P. SCHWARTZ (HFD-629) 301-594-1841 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAR-1997 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: _____

DMF No: _____

Responsibilities: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 28-FEB-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____

DMF No: _____

Responsibilities: _____

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

Establishment: **1823985**
L PERRIGO CO
8060 WHITBECK RD
MONTAGUE, MI 49437

DMF No:

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Profile: **SUP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 03-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **1811666**
PERRIGO CO
117 WATER ST
ALLEGAN, MI 49010

DMF No:

Responsibilities:
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 04-FEB-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

APPROVAL PACKAGE SUMMARY FOR 74-395

ANDA#: 74-395

FIRM: L. Perrigo Company

DRUG: Miconazole Nitrate

DOSAGE: Suppository

STRENGTH: 100 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is pending

BIO STUDY/BIOEQUIVALENCE STATUS: Bio study is acceptable 2/3/97

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C/80%RH and 12 months room temperature at 25°C for all the exhibit batches.

LABELING REVIEW STATUS: The labeling is satisfactory 2/26/96

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted copies of the exhibit batches lot #2T6450 using drug substance _____, lot #2V7407 using drug substance _____ by _____ and the _____ and lot #2X7402 using drug substance _____ and the _____
The exhibit batches were _____ using both drug substance _____ DMF. The DMF is satisfactory 5/17/94 and _____ DMF. The DMF is satisfactory 4/3/96.
The intended production batches will be _____. The firm will be using the same drug substance manufacturers and the same equipment and manufacturing procedures.

COMMENTS: The Application is Approvable Pending Acceptable EER.

REVIEWER: Nashed E. Nashed, Ph.D.

DATE: 2/26/97

SUPERVISOR: Paul Schwartz, Ph.D.

DATE: 2/28/97

ISI

3/3/97

ISI

3/3/97

Printed by Joseph Buccine
Electronic Mail Message

Confidentiality: COMPANY CONFIDENTIAL

Date: 05-Mar-1997 12:45pm
From: Robert West
WESTR
Dept: HFD-611 MPN2 273
Tel No: 301-594-1837 FAX 301-594-0183

TO: Joseph Buccine (BUCCINE)
CC: Mark Anderson (ANDERSONM)
CC: Gordon Johnston (JOHNSTONG)
Subject: RE: Perrigo's Miconazole Nitrate Vag Supps 74395

Joe:

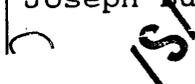
Thanks for the heads-up information. I've spoken to ViJay who has assured me that the bio signoff will occur within the next day (or so).

The office has determined that Dr. Williams does NOT need to sign off on bio studies with clinical endpoints such as this one. Dr. Fanning will be the signer. Arrangements are being made to do this.

Bob

**APPEARS THIS WAY
ON ORIGINAL**

RECORD OF TELEPHONE CONVERSATION

<p>Reference is made to our bio letter dated 2/6/97. In that letter, the sponsor was requested to develop comparative dissolution methods and specifications, and submit the data to the Agency for review asap.</p> <p>Immediately prior to this telecon, Mr. Buccine clarified with Dr. Patnaik and Dr. Park that an acceptable response to this request is not a precondition for approval. However, the sponsor must commit to responding to this request post approval. No response was received to date.</p> <p>The purpose of this telecon was to get Perrigo to agree to submit a commitment to develop dissolution methods and specifications, and submit the data to the Agency within a reasonable time frame post approval.</p> <p>Ms. Green agreed. Perrigo's commitment will be sent by FAX and followed by a hard copy to the file.</p> <p>cc: NDA Division File T-con Binder</p>	<p>DATE 3/5/97</p>
	<p>ANDA NUMBER 74-395</p>
	<p>IND NUMBER</p>
	<p>TELECON</p>
	<p>INITIATED BY FDA</p>
	<p>PRODUCT NAME Miconazole Nitrate Vaginal Suppositories, 100 mg</p>
	<p>FIRM NAME Perrigo</p>
	<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Virginia Green</p>
	<p>TELEPHONE NUMBER 616-673-7604</p>
	<p>SIGNATURE Joseph Buccine</p> <p align="right">  Y 3/5/97 </p>

T-Con

Miconazole Nitrate Vaginal Suppositories, 100 mg
Virginia Green (616) 673-7604
[REDACTED]

OGD 96-231
Bio 96-174
Perrigo

7/31/96: J. Gross *151*
Discussed the meeting request with Ms Green (see 7/28/96).
Told we should have the review back by the end of August but
that this was just an estimate.

7/29/96: J. Gross
left VMSG for Ms. Green

7/28/96: J. Gross

Virginia K. Green

The Office would like to acknowledge that the data submitted in response to our faxed-correspondence to you on April 18, 1996 has been received. The Agency is currently reviewing the data and currently we do not feel that a meeting is warranted at this time. If during the review of this application we feel that a meeting would be beneficial to resolve any further bioequivalence issues we hope that we would be able to request a meeting at such time.

Ms Green was not in I left a VMSG to RTN my call.

APPEARS THIS WAY
ON ORIGINAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration
ESTABLISHMENT EVALUATION REPORT
for March 04, 1997

Requestor's Name: JAMES, DANIEL S.

Division: DCI

Phone: 301-594-1841

Application: ANDA 74395

Brand Name:

Established Name: MICONAZOLE NITRATE

Strength: 100 MG VAGINAL

Dosage Form: SU

Sponsor: L PERRIGO

Org Code: 600 Priority:

Office:

Street: 117 WATER ST

City / State: ALLEGAN, MI 49010

District Goal: 04-OCT-94

Action Goal:

User Fee Goal:

Establishment: _____ Name: _____

Responsibilities

Dmf No

Profile

Status

Date

_____ CCS AC 28-FEB-97

Establishment: _____ Name: _____
IT

Responsibilities

Dmf No

Profile

Status

Date

_____ CCS AC 04-FEB-97

Establishment: 1823985 Name: L PERRIGO CO
8060 WHITBECK RD
MONTAGUE, MI 49437

Responsibilities

Dmf No

Profile

Status

Date

FINISHED DOSAGE MANUFACTURER SUP AC 03-MAR-97

Establishment: 1811666 Name: PERRIGO CO
117 WATER ST
ALLEGAN, MI 49010

Responsibilities

Dmf No

Profile

Status

Date

FINISHED DOSAGE RELEASE TESTER SUP PN 03-MAR-97
FINISHED DOSAGE STABILITY TESTER NEC AC 04-FEB-97

CSO

Date

Recommendation

FERGUSONS

03-MAR-97

ACCEPTABLE

COPY 2.1

DATE: NOV 29 1995

TO: Director, Detroit District, HFR-MW200

FROM: Chief
Investigations & Compliance Evaluation Branch, HFD-324

SUBJ: 10-Day Notification Applicant:
 ANDA 74-395, Miconazole L. Perrigo Co.
 Nitrate Vaginal 117 Water Street
 Suppositories USP Allegan, MI 49010
 100mg

Establishment:
L. Perrigo Co.
8060 Whitbeck
Montague, MI 49437

PROFILE: SUP

REVIEWER: D. James
TELEPHONE: 301-594-1841

CFN#: 1823985

The subject application, involving activities at the above referenced establishment in your District, has reached the approval stage in the Center for Drug Evaluation and Research. The application provides for this establishment to **manufacture and test** the above listed drug product. Based upon the current Quality Assurance Profile, and your earlier recommendation to approve this application, CDER does not intend to assign a pre-approval inspection. We know of no reason why final approval of the application should be withheld.

However, we will delay or withhold approval if warranted by ongoing inspection activities as provided in the memo of February 14, 1990 from the Director, Office of Compliance, CDER to all Districts, subject to "Procedure to request evaluations from Districts for all NDA/ANDAs".

Within 10 days, please advise the undersigned by FAX (301-827-0145), or EMS, whether or not approval should be withheld or delayed. Your reply should be in the prescribed format. Recommendations to withhold approval should be supported by EIR and exhibits sent to HFD-324 **within 30 days**.

Thank you for your attention.

for Mark A. Lynch *ISI*

Priority: **ANDA pending**

Target Completion:

cc:

HFD-324 ICEB R/F

DEC 9 1995

HFD-324 EER File

HFD-629 JAMES/WEIKEL

11/28/95:vsp

a:22187.FUR

MEMORANDUM

DATE: November 27, 1996

TO: Office of Generic Drugs
HFD-600
7500 Standish Place, room 150
Rockville, Maryland 20855

FROM: Andrea Meyerhoff MD.
Medical Officer, DAIDP, HFD-520

THROUGH: Brad Leissa MD ISJ 11/27/96
SMO, DAIDP, HFD-520

David Feigal MD ISJ 12-20-96
Director, DAIDP, HFD-520

SUBJECT: Consultation on ANDA 74-395

Please find attached to this memorandum, the medical consultation from HFD-520 which was requested. If there are any questions regarding this matter, please do not hesitate to contact the Division at 827-2120. Thank you for this consultation.

APPEARS THIS WAY
ON ORIGINAL

File Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
---	---------------------------------

TO (Division/Office) HFD-520 Division of Anti-infective Drug Prod	FROM: HFD-650 Division of Bioequivalence
--	---

DATE 3/27/96	IND NO.	NDA NO. N 74-395	TYPE OF DOCUMENT Study Amendment	DATE OF DOCUMENT 3/21/96
-----------------	---------	---------------------	-------------------------------------	-----------------------------

NAME OF DRUG Miconazole Nitrate Suppos	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 45 Days
---	------------------------	------------------------	------------------------------------

NAME OF FIRM
 Perrigo

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY _____ | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (Specify below) |
|--|--|---|

II. BIOMETRICS

- | | |
|--|---|
| <p style="text-align: center;">STATISTICAL EVALUATION BRANCH</p> <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER | <p style="text-align: center;">STATISTICAL APPLICATION BRANCH</p> <input type="checkbox"/> CHEMISTRY
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER |
|--|---|
- S. 302
BONA

III. BIOPHARMACEUTICS

- | | |
|---|---|
| <input type="checkbox"/> ISSOLUTION
<input type="checkbox"/> AVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL- BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|---|

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL
 PRECLINICAL

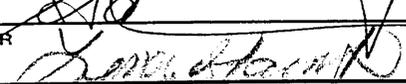
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

For review by Dr. Julius Piver

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

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

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

SIGNATURE OF REQUESTER 	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER 	SIGNATURE OF DELIVERER

2/20/96

MEMORANDUM

DATE: November 27, 1996

TO: Office of Generic Drugs
HFD-600
7500 Standish Place, room 150
Rockville, Maryland 20855

FROM: Andrea Meyerhoff MD
Medical Officer, DAIDP, HFD-520

THROUGH: Brad Leissa MD ISI 11/27/96
SMO, DAIDP, HFD-520

David Feigal MD ISI 12-20-96
Director, DAIDP, HFD-520

SUBJECT: Consultation on ANDA 74-395

Please find attached to this memorandum, the medical consultation from HFD-520 which was requested. If there are any questions regarding this matter, please do not hesitate to contact the Division at 827-2120. Thank you for this consultation.

APPEARS THIS WAY
ON ORIGINAL

Division of Anti-Infective Drug Products

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

FACSIMILE TRANSMISSION

DATE: 3.6.96 Number of Pages (including cover sheet) 9

TO: Jason Gross

COMPANY: Office of Generic Drugs

FAX NUMBER: 301 594-0181

MESSAGE: Here is the information requested on ANDA 74-395 (Perrigo)

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

FROM: Julius Piver, M.D.

TITLE: Medical Officer

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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

BASELINE

1ST REVISIT

2ND REVISIT

Treatment-Perrigo

Subject	MOH	CULT	Symptoms	MOH	CULT	Symptoms	#Days*	MOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
1	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	39
2	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	42
6	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
8	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
11	Pos	Pos	Severe	Pos	Pos	None	15	-	-	-	No	No	-
14	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
16	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
19	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	39
20	Pos	Pos	Severe	Neg	Pos	None	14	-	-	-	No	No	-
X 22	Pos	Pos	Mild	Neg	Pos	None	28	X	-	-	No	No	42
22	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	43
30	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
36	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	None	No	Yes	43
37	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Pos	None	No	Yes	42
39	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	36
X 42	Pos	Pos	Moderate	Neg	Neg	Mild	23	X	Neg	None	Yes	Yes	45
44	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
X 45	Pos	Pos	Mild	Neg	Neg	None	22	X	Neg	None	Yes	Yes	47
47	Pos	Pos	Moderate	Neg	Neg	Mild	22	Neg	Neg	Mild	Yes	No	47
50	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
51	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
60	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
63	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
64	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
66	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Pos	None	No	Yes	36
69	Pos	Pos	Severe	Neg	Pos	None	20	-	-	-	No	No	-
74	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
79	Pos	Pos	Severe	Neg	Neg	None	15	Pos	Pos	None	No	Yes	36
81	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	36
83	Pos	Pos	Moderate	Neg	Neg	None	13	Neg	Neg	None	Yes	Yes	36
85	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37

* Number of days post-treatment to review

(14)

X

MAY 18 '95

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Keonistat-7 r
 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

1ST REVISIT

2ND REVISIT

Treatment-Perrigo
(continued)

Subject	ROI	CULT	Symptoms	KOR	CULT	Symptoms	#Days*	KOR	CULT	Symptoms	Mycol cure	Clin cure	#Days*
87	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	42
89	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	35
91	Pos	Pos	Moderate	Neg	Neg	None	11	Neg	Neg	None	Yes	Yes	39
93	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	41
95	Pos	Pos	Severe	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	43
97	Pos	Pos	Mild	Neg	Pos	None	21				No	No	
98	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
102	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
104	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	41
105	Pos	Pos	Moderate	Neg	Pos	None	15	Pos	Pos	Mild	No	No	43
110	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
119	Pos	Pos	Severe	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	43
X 122	Pos	Pos	Moderate	Neg	Neg	None	24	X	Neg	None	Yes	Yes	45
124	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
126	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
127	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
X 129	Pos	Pos	Mild	Neg	Neg	None	22	X	Neg	None	Yes	Yes	45
130	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	38
131	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
X 134	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	46
137	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
X 138	Pos	Pos	Mild	Neg	Neg	None	27	X	Neg	None	Yes	Yes	49
142	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	42
144	Pos	Pos	Mild	Neg	Pos	None	20				No	No	
145	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
147	Pos	Pos	Mild	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	42
148	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	Mild	No	No	40
X 152	Pos	Pos	Moderate	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	50
156	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
157	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Pos	None	No	Yes	43

* Number of days post-treatment to review

(5)

X

30



Comparison of Miccnazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis

Project Number 901368

All eligible enrolled patients, by treatment group

BASLINE

1ST REVISIT

2ND REVISIT

Treatment-Perrigo (continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
X 158	Pos	Pos	Severe	Neg	Neg	None	22	X	Neg	None	Yes	Yes	45
161	Pos	Pos	Severe	Neg	Neg	None	22		Pos	None	No	Yes	43
X 162	Pos	Pos	Moderate	Neg	Neg	None	22	X	Neg	Mild	No	NO	45
X 165	Pos	Pos	Mild	Neg	Neg	None	22	X	Neg	None	Yes	Yes	47
166	Pos	Pos	Moderate	Neg	Neg	None	21		Neg	None	Yes	Yes	44
172	Pos	Pos	Moderate	Neg	Neg	None	13		Pos	None	No	Yes	41
173	Pos	Pos	Moderate	Neg	Neg	None	15		Neg	None	Yes	Yes	45

(3)

APPEARS THIS WAY ON ORIGINAL

* Number of days post-treatment to review

✓

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

Date: 04-Mar-1996 02:26pm EST
From: Jason Gross
GROSSJ
Dept: HFD-615 MPN2 113
Tel No: 301-594-2290 FAX 301-594-0181

TO: Julius Piver

(PIVERJ)

Subject: Miconazole, Perrigo

Dr. Piver

Perrigo would also like a list of the 19 subjects that were excluded based on the time frame issue.

ANDA 74-395
L. Perrigo Co.
Miconazole Nitrate Vaginal Suppositories, 100 mg.

The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo-group and 55 in

Thanks
JAG

APPEARS THIS WAY
ON ORIGINAL

Enclonaz

~~17.164~~ ~~17.164~~ ~~17.164~~ - 1 -

Pt #	Eval	First Visit		Second Visit		Thera- peutic out.
		Myco	Clin	Myco	Clin	
22	—	F	C (28)	F	C (42)	
45	—	C	C 22	C	C (47)	—
47	"	C	C 22	C	F (47)	"
42	—	C	C (23)	C	C (45)	
122	—	C	C (29)	C	C (45)	
124	"	C	C 22	C	C (45)	
134	"	C	C 20	C	C (48)	
138	"	C	C (27)	C	C (49)	
152	—	C	C 16	C	C (50)	
158	—	C	C 22	C	C (45)	
163	"	C	C 22	F	R (45)	
165	"	C	C 22	C	C (47)	

APPEARS THIS WAY
ON ORIGINAL

34

Comparison of Nicotazole 100 mg Suppositories (Perrigo) and Monistat-7 (Ortho) in the Treatment of Vulva-Vaginal Candidiasis
 Project Number 901369
 All eligible enrolled patients, by treatment group

-----Treatment-Ortho-----
 (continued)

Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Nycol cure	Clin cure	#Days*
80	Pos	Pos	Severe	Neg	Yeg	None	20	Neg	Neg	None	Yes	Yes	41
82	Pos	Pos	Moderate	Neg	Neg	None	13	Neg	Neg	None	Yes	Yes	34
84	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Pos	None	No	Yes	36
88	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
92	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	36
94	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	34
95	Pos	Pos	Mild	Neg	Neg	None	23	Neg	Pos	None	No	Yes	44
99	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
100	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	42
111	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	35
X 112	Pos	Pos	Severe	Neg	Neg	None	25	Neg	Neg	None	Yes	Yes	48
121	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
123	Pos	Pos	Moderate	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	41
128	Pos	Pos	Mild	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	41
132	Pos	Pos	Mild	Neg	Neg	None	18	Neg	Pos	None	No	Yes	44
135	Pos	Pos	Mild	Pos	Neg	None	21	Neg	Neg	None	No	Yes	41
139	Pos	Pos	Moderate	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	43
140	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	43
146	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	46
X 147	Pos	Pos	Moderate	Neg	Neg	None	20	Neg	Neg	None	No	Yes	44
148	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Pos	None	No	Yes	45
148	Pos	Pos	Mild	Neg	Neg	None	18	Neg	Pos	None	No	Yes	45
150	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Pos	None	No	Yes	45
X 151	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Pos	None	No	Yes	45
159	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
X 160	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	47
X 166	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	47
X 166	Pos	Pos	Mild	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	45
171	Pos	Pos	Severe	Neg	Neg	None	21	Neg	Neg	None	Yes	Yes	44
171	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	41

* Number of days post-treatment to review

(5)

X

BASLINE

1ST VISIT

2ND VISIT

Treatment-Ortho

Comparison of Miconazole 100 mg Suppositories (Perrigo) and Moxidectin (Ortho) in the Treatment of Vulvo-Vaginal Candidiasis
 Project Number 901368
 All eligible enrolled patients, by treatment group

Subject	ROH	CULT	Symptoms	ROH	CULT	Symptoms	#Days*	ROH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
3	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
4	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
5	Pos	Pos	Severe	Neg	Neg	None	19	Neg	Neg	None	Yes	Yes	37
7	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	42
10	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
12	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
13	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	35
15	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	38
17	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	No	Yes	37
18	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	35
23	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	39
X 24	Pos	Pos	Moderate	Pos	Pos	Mild	15	Neg	Neg	None	Yes	Yes	43
25	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	No	No	50 X
17	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	43
17	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	38
17	Pos	Pos	Moderate	Neg	Neg	Mild	15	Neg	Neg	None	Yes	Yes	36
14	Pos	Pos	Mild	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	37
18	Pos	Pos	Mild	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	42
40	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	40
41	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
43	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
45	Pos	Pos	Mild	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	44
48	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
48	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
53	Pos	Pos	Moderate	Pos	Pos	Moderate	20	Neg	Neg	None	Yes	Yes	44
59	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	No	No	36
61	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
62	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
62	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
65	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
72	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	No	Yes	43
75	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	No	Yes	42
75	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
75	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	35

* Number of days post-treatment to review

10

X

FILE

Division of Anti-Infective Drug Products

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

FACSIMILE TRANSMISSION

DATE: 3.6.96 Number of Pages (including cover sheet) 9

TO: Jason Gross

COMPANY: Office of Generic Drugs

FAX NUMBER: 301 594-0181

MESSAGE: Here is the information requested on ANDA 74-395 (Perrigo)

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

FROM: Julius Piver, M.D.

TITLE: Medical Officer

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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

2

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

Date: 04-Mar-1996 02:26pm EST
From: Jason Gross
GROSSJ
Dept: HFD-615 MPN2 113
Tel No: 301-594-2290 FAX 301-594-0181

TO: Julius Piver

(PIVERJ)

Subject: Miconazole, Perrigo

Dr. Piver

Perrigo would also like a list of the 19 subjects that were excluded based on the time frame issue.

ANDA 74-395
L. Perrigo Co.
Miconazole Nitrate Vaginal Suppositories, 100 mg.

The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo-group and 55 in
Thanks
JAG

APPEARS THIS WAY
ON ORIGINAL

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

Date: 23-Feb-1996 01:48pm EST
From: Mark Anderson
ANDERSONM
Dept: HFD-617 MPN2 113
Tel No: 301-594-0360 FAX 301-594-3839

TO: Paul Schwartz (SCHWARTZP)
TO: Daniel James (JAMESD)
TO: Anna Weikel (WEIKELA)
CC: Robert West (WESTR)

Subject: Perrigo 74-395 Bio Deficiency

Paul/Dan/Anna Marie:

Bio issued the attached letter to Perrigo today. Their response will need to be considered as a major as it appears they will need to do a new study.

M--k

LETTER SENT 2/23/96

ANDA 74-395

L. Perrigo Co.
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

Dear Madam:

This is in reference to your abbreviated new drug application for Miconazole Nitrate Vaginal Suppositories, 100 mg.

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

The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based

on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo- group and 55 in the Ortho-group).

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

Group	Visit 2 Agency [Perrigo]	Visit 3 Agency [Perrigo]
Mycological Cure Rate		
Perrigo	51/56 [62/68]	40/56 [50/63]
Ortho	52/55 [58/62]	44/55 [48/60]
Clinical Cure Rate		
Perrigo	55/56 [68/68]	47/56 [55/64]
Ortho	54/55 [61/62]	50/55 [56/60]
Therapeutic Cure Rate Visit 3		
Perrigo	40/56 [48/68]	Agency [Perrigo]
Ortho	43/55 [47/62]	

3. The Agency evaluated the data based on 111 evaluable subjects as summarized above and concluded that:

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

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

3. The summary report, IRB approval letter, drug composition statement, nor the product formulation data documented the product Lot number used in the study. The lot numbers, 2T6450 for the test and 22A125 for Ortho product were recorded only in the protocol. In future the Lot numbers of products used should be properly recorded on all forms.

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

Sincerely yours,

APPROVAL SUMMARY

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

Date of Review: 2/7/96 Date of Submission: 12/18/95

Primary Reviewer: Lillie D. Golson

Secondary Reviewer: Carol Zimmerman

ANDA Number: 74-395

Review Cycle: #4

Applicant's Name [as seen on 356(h)]: Perrigo Company

Manufacturer's Name (If different than applicant): Same

Proprietary Name: None

Established Name: Miconazole Nitrate Vaginal Suppositories USP,
100mg

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: Unit-dose suppository (100 mg) - December
18, 1995

Carton Labeling: 1 X 7s - December 18, 1995

Patient Package Insert Labeling: December 18, 1995 (revised
11/95)

Revisions needed post-approval:

1. CONTAINER

Add manufacturer's name and address

2. EDUCATIONAL BROCHURE

a. WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?

- i. Revise the ultimate sentence of paragraph 2 to read ...most often in ~ women who... (add some)
- ii. Revise sentences 4 and 5 of paragraph 3 to read ...infections or, ~ vaginal yeast... (add ' ~ as per most currently approved insert labeling of 2/95)

Note: In labeling review dated 12/2/94, we asked that " ~ " be deleted. Since it's included the latest approved labeling, we're asking them to put it back in.

b. FOR BEST RESULTS

Delete "or urination" from Number 6 to be consistent with the innovator.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Monistat® 7 Vaginal Suppositories

NDA Number: 17-450

NDA Drug Name: same as RLD

NDA Firm: Advanced Care Products

Date of Approval of NDA Insert and supplement #'s 038 and 039: February 9, 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: NDA 17-450

Basis of Approval for the Carton Labeling: NDA 17-450

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	N o	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			
<i>PROPRIETARY NAME</i>			
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
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
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	
<i>LABELING</i>			
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
Error Prevention Analysis: 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.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			X
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) Page 52			
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) USP - 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 innovator.			

DATE: December 5, 1995

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

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

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

Mary Fanning, M.D., PH.D. *ISI* 12/13/95
Director, DAIDP, HFD-520

SUBJECT: Consultation on ANDA 74-395

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

Thank you for this consultation.

*Perrigo
Miconazole NO3
9/1/93 7/30 - Rec'd 8/4/93 SPS*

APPEARS THIS WAY
ON ORIGINAL

File 74-395

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE November 30, 1995						
<p>I spoke with Jackie Eaton regarding the chemistry status of this application. She inquired about withdrawing the DMF for the inactive. (The DMF holder, _____ had just been issued a DMF deficiency letter in Nov. 1995, and the DMF holder is expected to answer the letter around Jan '96.)</p> <p>I told her that we were not in favor of them withdrawing the DMF for the inactive at this point because the DMF has been found to be deficient. Although we acknowledge that the submission of this Type IV DMF is not an official requirement, if this deficient DMF is withdrawn, a new source must be used.</p> <p>I also pointed out that it is estimated that the bio consult will not be expected back here until January 1996, at the earliest, per Cecilia. So it appears that the responses to the DMF and the bio consult will coincide in the end, from a timing standpoint.</p> <p>She responded that Perrigo will try to work with the DMF holder to try and hasten their response.</p> <p>She thanked me for the information and the conversation terminated amicably.</p> <p style="text-align: center;">APPEARS THIS WAY ON ORIGINAL</p>	ANDA NUMBER 74-395						
	SUPPLEMENT NUMBER						
	TELECON/MEETING						
	<table border="1"><tr><td>INITIATED BY</td><td>MADE</td></tr><tr><td><input checked="" type="checkbox"/> APPLICANT/ SPONSOR</td><td><input checked="" type="checkbox"/> BY TELEPHONE</td></tr><tr><td><input type="checkbox"/> FDA</td><td><input type="checkbox"/> IN PERSON</td></tr></table>	INITIATED BY	MADE	<input checked="" type="checkbox"/> APPLICANT/ SPONSOR	<input checked="" type="checkbox"/> BY TELEPHONE	<input type="checkbox"/> FDA	<input type="checkbox"/> IN PERSON
	INITIATED BY	MADE					
<input checked="" type="checkbox"/> APPLICANT/ SPONSOR	<input checked="" type="checkbox"/> BY TELEPHONE						
<input type="checkbox"/> FDA	<input type="checkbox"/> IN PERSON						
PRODUCT NAME Miconazole Nitrate Vaginal Suppository 100 mg							
FIRM NAME L. Perrigo							
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Jackie Eaton							
TELEPHONE (616) 673 - 7670							
SIGNATURE 	VERSION HFD-617						

Redacted

13

pages of trade secret and/or

confidential

commercial

information

DATE: JAN 13 1994

Assignment # 94-84

TO: Director, Detroit District Office, HFR-MW200

To: H. P. Ewing

FROM: Chief Investigations & Compliance Evaluation Branch, HFD-324

SUBJ: Inspection Request
ANDA 74-395
Miconazole Nitrate
Vaginal Suppositories
100mg

Applicant:
L. Perrigo Company
117 Water Street
Allegan, MI 49010

- For inspection.

MAZ
1/14/94

Establishment:
L. Perrigo Company
117 Water Street
Allegan, MI 49010

Target Completion
date: Feb 13, 1994

PROFILE: ~~668~~-SOP

REVIEWER: William Russell
TELEPHONE: 301/594-0315 XEEA

copy: FF
City: account
file

In connection with FDA's review of ANDA 74-395, please conduct a CGMP inspection of the referenced establishment. The application provides for this establishment to perform testing for the above referenced drug product. For guidance, refer to CP 7346.832, Pre-Approval Inspections.

This application cannot be acted upon until the inspection is completed and your findings are reported to this office. Please call well in advance if you are unable to meet the time frame, whether due to priorities or the lack of readiness on the part of the firm.

In preparing this assignment, we relied on the MPOAS drug quality assurance profile which reports that the referenced establishment was never inspected for drug products in the referenced profile class. If there has been recent coverage, or if the profile or location is not accurate, please call FTS 301/594-0098, within one week to discuss the need for the inspection and update the QAP through the usual means.

Upon completion of this assignment, please provide this office with a copy of the EIR endorsement (FDA 481(E)-(CG)). If this inspection is classified OAI, include a recommendation to withhold application approval and full documentation of CGMP violations. If the district expects delays in completing a non-violative EIR, notify this office of the inspection findings by EMS.

In communicating with this office reference should be made to the above ANDA number. Please direct your written response to the attention of the Investigations & Compliance Evaluation Branch, HFD-324.

for
S/
Mark A. Lynch

Priority: ANDA pending
Target Completion: FEB 13 1994

MASTER FILE
COMMITMENTS

APPEARS THIS WAY
ON ORIGINAL

Redacted

56

pages of trade secret and/or

confidential

commercial

information

October 6, 1994 (ds)

Telephone Conversation Between Doug Sporn and Jackie Eaton

JE had called in reference to ANDA 74-95, miconazole nitrate suppository 100 mg. JE said she understood that the chemistry review was coming to an end and that it was currently with a supervisor. She pointed out that the bio submission had been with the Center for 425 days and asked if there was anything they could do to speed the process along. DS explained that consults such as this have to go to New Drugs where OGD has one half of an FTE devoted to reviewing such studies. DS said the work that is in New Drugs is there on a priority basis and Perrigo's study would have to wait its turn to be reviewed. He indicated that the best the firm could hope for would be that its next letter from OGD would be one indicating there are no further chemistry deficiencies or that it was in minor amendment status. He indicated that if this happens, the medical reviewer will be notified that the application has priority. However, if there are other minor amendments pending that are older than Perrigo's they would be reviewed ahead of the firm's.

JE said she had been told that the medical reviewer was working on user fee applications and, therefore, he had to give greater attention to that. DS indicated that was not entirely the case because the Office had provided part of a FTE for this person to work under so he could devote at least half of his time to OGD applications. She inquired if there was a way for the firm to pay user fees so their application could get reviewed. DS said that would require implementing legislation which Generic Drugs currently did not have.

She inquired as to how many applications were ahead of Perrigo's and how old they were. DS said he would not want to divulge the number of applications ahead of Perrigo's other than to say there were some and some of these were in minor amendment status but that could change on a day-to-day basis. DS also said he did not want to speculate on the age of other studies that were in the queue but he did know that there have been studies that have been fairly old. DS closed by saying that JE was welcome to call him back after she had gotten the latest chemistry letter response from OGD or she could wait a month to call back and at that time DS would try to let her know if anything had changed as far as the priority of the bio review. (D. Sporn)

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REVIEW OF PROFESSIONAL LABELING #3

Original

FPL

DATE OF REVIEW: December 2, 1994

ANDA #: 74-395

NAME OF FIRM: Perrigo Company

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

DATE OF SUBMISSION: November 15, 1994

COMMENTS:

Container:

Revise to read, "...Suppository...", (singular).

Carton:

1. We acknowledge your comments regarding the tamper resistant packaging for your product.
2. Delete the word, " ", from your storage recommendations, e.g., "Store at room...".
3. Increase the print quality of your final printed labeling.

Patient Package Insert:

1. Please submit final printed patient package insert labeling which is printed on both sides.
2. See comment 2. under Carton.
3. WHAT ARE VAGINAL...

In paragraph three, delete " " where it precedes "vaginal yeast infections", (two places).

4. WARNINGS

Delete the word in the first sentence.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels, carton labeling, and patient package insert, then prepare and submit final printed labeling.

FOR THE RECORD:

1. Review based on labeling of Advanced Care Product's labeling approved 10/8/92 for Monistat® 7 Vaginal Suppositories.
2. Storage Recommendation:

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

USP: Preserve in tight containers, at controlled room temperature.

Perrigo: Store at controlled room temperature 15°-30°C (59°-86°F). Avoid heat (over 30°C or 86°F).
3. Inactive Ingredients: Hydrogenated vegetable oil (applicant and innovator).

Charles Hoppes

cc: ANDA 74-395
HFD-613/CHoppes/JWhite/JPhillips (no cc)
njg/01/06/94/74395NOV.94
Review
final

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

<p>Reference is made to our bio letter dated 2/6/97. In that letter, the sponsor was requested to develop comparative dissolution methods and specifications, and submit the data to the Agency for review asap.</p> <p>Immediately prior to this telecon, Mr. Buccine clarified with Dr. Patnaik and Dr. Park that an acceptable response to this request is not a precondition for approval. However, the sponsor must commit to responding to this request post approval. No response was received to date.</p> <p>The purpose of this telecon was to get Perrigo to agree to submit a commitment to develop dissolution methods and specifications, and submit the data to the Agency within a reasonable time frame post approval.</p> <p>Ms. Green agreed. Perrigo's commitment will be sent by FAX and followed by a hard copy to the file.</p> <p>cc: NDA Division File T-con Binder</p>	DATE 3/5/97
	ANDA NUMBER 74-395
	IND NUMBER
	TELECON
	INITIATED BY FDA
	PRODUCT NAME Miconazole Nitrate Vaginal Suppositories, 100 mg
	FIRM NAME Perrigo
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Virginia Green
	TELEPHONE NUMBER 616-673-7604

June 20, 1994 (ds)

Telephone Conversation Between Doug Sporn and Fred Radford of Perrigo Regarding ANDA 74-395, Miconazole Nitrate Vaginal Suppository, 100 mg

DS called FR as follow up to their conversation of the previous Friday (see comlog note above). DS explained that the firm's bio study had been sent to HFD-520 on September 1, 1993, that it was in queue, and there are several applications ahead of it, some of which are minor amendments and will receive priority. DS also explained that HFD-520 had a new medical reviewer on board who would take some amount of time to get up to speed in reviewing our bio consults.

DS indicated that the best the firm could hope for would be that the next response to the material they had submitted as a major amendment would be reviewed and found to be suitable as a minor amendment. If this comes to be, then Perrigo's application, i.e., bio study, may become a higher priority in the review process.

FR said he had understood from John Dawson, CSO, that the Office would not review the chemistry amendment until the bio study was completed. DS said he did not think this was the case but he would check. Subsequently, Bob Pollock spoke to John Dawson and he confirmed that there apparently had been some misunderstanding on the part of Perrigo. In fact, the chemistry review will continue and will not be held up pending the review of the bio submission.

FR inquired exactly when HFD-520 would be notified that their application was in the minor amendment status if, in fact, that happened. DS said that the Division would be notified at the time OGD made an official determination that the firm's next response to a not approvable letter would be a minor amendment. DS also indicated that if it turned out that all deficiencies had been sufficiently answered in this current major amendment, then HFD-520 would also be notified that an application was pending approval and the bio study could possibly receive higher priority in the review process.

FR inquired if DS could give him a time frame for when the review might take place. DS indicated that he could not. FR inquired whether he could get an estimate of the number of applications that were ahead of Perrigo's. DS said he could not give him a specific estimate but indicated that it was a handful. DS also said that if the firm had not heard anything in a month, FR could call DS back. At that time, DS may or may not have any additional information that he could impart to the firm.

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June 16, 1994 (sms)

Ed Radford of Perrigo, DSporn and SSheehan had a telecon to discuss Mr. Radford's request for the status of the bioequivalence review of ANDA 74-395, Miconazole Nitrate Vaginal Suppository, 100 mg. DSporn explained that these types of drug products are sent to the Offices of Drug Evaluation for consult and that Office is backed up with reviews. Applications at minor amendment stage have highest priority. The firm provided a major amendment response on March 8, 1994. OGD to check status and respond to firm.

(After the telecon SSheehan confirmed that the ANDA was sent to HD-520 for review on September 1, 1993 and that it is sixth in line for review as of June 17, 1994. See note01 this directory.)

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING #2

Original

DRAFT

DATE OF REVIEW: April 7, 1994

ANDA #: 74-395

NAME OF FIRM: Perrigo

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

DATE OF SUBMISSION: March 8, 1994

COMMENTS:

General:

Revise the established name of your product on all labels and labeling as follows: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

Container:

See general comment above (relocate the comma).

Carton:

1. The innovator utilizes a printed seal for both end flaps of the carton. You have directed the consumer to inspect the plastic unit for signs of tampering. Although only one tamper resistant feature is required by 21 CFR 211.132, we would encourage you to consider a similar design as the listed drug.
2. See general comment above

Insert:

1. Please revise the established name of your product in the title of the insert as requested in the general comment above.
2. In the section "WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?:

 Italicize "*Candida*" where it appears.
3. We acknowledge that we had requested that the entire "ADVERSE REACTIONS (SIDE EFFECTS)" section be deleted. Based on the listed drug's most current approved labeling,

however, we request that you add this section back into your package insert as it appeared in your July 30, 1993, submission.

4. After the "FOR BEST RESULTS" section, add a new section as follows:

IF YOU HAVE A QUESTION

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

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their container labels, carton labeling, and patient package insert, then prepare and submit final printed labeling or draft labeling if they prefer.

FOR THE RECORD:

1. Review based on labeling of Advanced Care Product's labeling approved 10/8/92 for Monistat[®] 7 Vaginal Suppositories.
2. Storage Recommendation:

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

USP: Preserve in tight containers, at controlled room temperature.

Perrigo: Store at controlled room temperature 15-30°C (59-86°F). Avoid heat (over 30°C or 86°F).
3. Inactive Ingredients: Hydrogenated vegetable oil (applicant and innovator).

Charles Hoppes

cc: ANDA 74-395
HFD-613/CHoppes/MGonitzke (no cc)
njg/5/26/94/74395
Review
final

ISI 5/26/94
ISI 5/31/94

Insert: Not Satisfactory

1. **Headline**

Include the suppository strength: VAGINAL
SUPPOSITORIES, USP 100 mg

2. **WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?**

"...(hearing impaired, TDD).

3. **SYMPTOMS OF VAGINAL YEAST INFECTIONS**

"...of a vaginal yeast infection. They can..."

4. **WARNINGS**

a. The WARNINGS section is highlighted in a
contrasting BOXED color by the listed drug. Your
labeling should be similar in prominence.

b. "...recurrent vaginal infections,..."

c. Delete sentence: "If your doctor has
previously..."

5. **CONTENTS**

"...100 mg of miconazole..."

6. **DIRECTIONS FOR USE**

Under "3" : "As shown in the pictures, this..."

7. **ADVERSE REACTIONS (SIDE EFFECTS)**

Delete entire section.

8. **FOR BEST RESULTS**

"...bowel movement or urination."

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their labels and labeling, then prepare and submit draft labels and labeling.

3. FOR THE RECORD

Deletion in the WARNINGS section and the deletion of the ADVERSE REACTIONS section is based on an "approved" supplement dated November 25, 1991, for MONISTAT for which we only have draft labeling.

Charles Hoppes

CC:

ANDA 74-395

HFD-613/CHOPPES/JPHILLIPS (no cc)

mpd/1/31/94/74395JUL.93

Review

Final

[Handwritten initials and dates]
1/31/94
2/1/94

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-395

CORRESPONDENCE



March 7, 1997

NEW CORRESP

NC

Office of Generic Drugs, OPS, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Mr. Douglas Sporn, Director

Telephone Amendment

**RE: Miconazole Nitrate Vaginal Suppositories, 100 mg
ANDA 74-395**

Dear Mr. Sporn:

This letter is in response to the Agency's communication dated February 6, 1997 from the Division of Bioequivalence regarding the L. Perrigo Company's Miconazole Nitrate Vaginal Suppositories, 100 mg application.

Within the 02/06/97 communication, the Division of Bioequivalence requested that the L. Perrigo Company develop comparative dissolution methods (test *versus* reference) and specifications using 12 units. This request was further clarified by Elizabeth Sanchez of the Office of Generic Drugs on 02/13/97 with Brian Schuster of the L. Perrigo Company as being a post-approval request which did not require action prior to approval.

However, on March 5, 1997, Mr. Joe Buccini of the Office of Generic Drugs contacted Virginia Lutke of the L. Perrigo Company requesting that, prior to approval of the application, a commitment be submitted to develop these dissolution methods and specifications. The L. Perrigo Company is in the process of acquiring the instrumentation needed to perform the analysis and expects to be in a position to begin the development work in the near future. The L. Perrigo Company commits to providing information on the progress of the development effort in the first annual report, or sooner if the investigation is completed before that time.

If you have any questions or need any additional information, please feel free to contact me by telephone at 616-673-7604, by fax at 616-673-7655 or e-mail at GLUTKE@PERRIGO.COM.

Respectfully,

Virginia G. Lutke
Regulatory Affairs

xc: B. Schuster
G. Boerner

RECEIVED

MAR 10 1997

GENERIC DRUGS

**REGULATORY AFFAIRS DEPARTMENT****Fax: 616-673-7655****FACSIMILE TRANSMISSION****DATE: March 7, 1997****TO: Mr. Joe Buccini
FAX # 1-301-594-0180****COMPANY: FDA, Office of Generic Drugs****FROM: Ginger Lutke****TEL. # 616-673-7604****CC:****NUMBER OF PAGES (INCLUDING COVER PAGE) 2****MESSAGE:****RE: ANDA 74-395 Miconazole Nitrate Vaginal Suppositories, 100 mg**

Please call Lee McGinnis at (616) 673-7603 if there are transmission problems.

CONFIDENTIALITY NOTE: The documents accompanying this telecopy transmission contain information belonging to the Perrigo Company which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us.



orig

CONFIRMATION COPY

October 21, 1996
VIA FAX 1-301-594-1174

Jason A. Gross, Pharm. D.
FDA, Office of Generic Drugs
Division of Bioequivalence
7500 Standish Place, HFD 612
Rockville, MD 20855

RE: ANDA 74-395 Miconazole Nitrate 7 Day Suppositories

Dear Dr. Gross:

NEW SERIES

This letter authorizes the FDA to discuss the biostudy review status with the _____
_____ law firm for the above referenced application.

If you have any questions or need further information regarding this matter, please feel free to contact me at 616-673-7604 or fax 616-673-7655.

Respectfully,

Virginia K. Green

Virginia K. Green
Sr. Regulatory Affairs Administrator

RECEIVED

OCT 23 1996

cc: J. Eaton
Alan Minsk - Hyman, Phelps, McNamara

GENERIC DRUGS



Noted - ISI
4/30/96
Copy to
Tad
7/16/96
ISI

NEW CORRESP

APR 25 1996

April 24, 1996
VIA FEDERAL EXPRESS

APR 25 1996

Office of Generic Drugs, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Julius Piver M.D.
Medical Officer

GENERIC DRUGS

RE: Miconazole Nitrate Vaginal Suppositories, 100mg
ANDA 74-395

Dear Dr. Piver:

This letter is in response to your facsimile communication dated April 18, 1996. In that communication, you requested several summary tables for Perrigo's bioequivalence study for ANDA 74-395 Miconazole Nitrate Vaginal Suppositories, 100 mg be reformatted to indicate visits 2 and 3. The reformatted tables are enclosed per your request.

The Perrigo Company, along with _____ would like to meet with the Agency to discuss and resolve any concerns with this application in order to expedite review and approval. Please contact me by telephone at (616) 673-7604 or by FAX at 616-673-7655.

Respectfully submitted,

Virginia K. Green

Virginia K. Green
Regulatory Affairs

enc.

cc: J. Eaton
D. Jespersen
E. Pileggi

5-16-96
D
SI



CONFIRMATION COPY

me842
BIOAVAILABILITY

NEW CORRESP

March 28, 1996
VIA FAX

Office of Generic Drugs, OPS, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Julius S. Piver, M.D.
Medical Officer

RE: Miconazole Nitrate Vaginal Suppositories, 100 mg - ANDA 74-395 ✓
Miconazole Nitrate Vaginal Cream 2% - ANDA 74-760

Dear Dr. Piver:

The Perrigo Company filed an amendment for ANDA 74-760 Miconazole Nitrate Vaginal Cream 2% on 3/20/96 to reformat the data for the bioequivalence study. The Perrigo Company filed a major amendment for ANDA 74-395 Miconazole Nitrate Vaginal Suppositories on 3/21/96, also for the bioequivalence study.

The purpose of this communication is to respectfully request that the Perrigo Company's amendment dated 3/21/96 for ANDA 74-395 be reviewed prior to Perrigo's amendment dated 3/20/96 for ANDA 74-760.

Please contact me by telephone at 616-673-7604 or by FAX at 616-673-7655 if you have any questions or need any additional information. The Perrigo Company thanks you for your prompt review of these applications.

Respectfully submitted,

Virginia K. Green

Virginia K. Green
Regulatory Affairs

cc: J. Eaton
D. Jespersen
E. Pileggi
C. Parise (OGD)

Smith Piver

DM 3/29/96

MAR 29 1996

46-92-4-26-40
IS

PERRIGO®

Orig

BIOAVAILABILITY
Dy 15 R10

RECEIVED

MAR 22 1996

GENERIC DRUGS

March 21, 1996
VIA FEDERAL EXPRESS

Office of Generic Drugs, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Keith K. Chan, Ph.D.
Director, Div. of Bioequivalence

EXPEDITED REVIEW REQUESTED
MAJOR AMENDMENT

RE: Miconazole Nitrate Vaginal Suppositories, 100mg
ANDA 74-395
MAJOR AMENDMENT

ORIG NEW CORRES.

Dear Dr. Chan:

This letter is in response to the Agency's communication dated February 23, 1996. In that letter, the Agency commented on Perrigo's bioequivalence study for ANDA 74-395 Miconazole Nitrate Vaginal Suppositories, 100 mg.

In a letter to the Agency dated March 11, 1996, the Perrigo Company stated they would respond to the Agency's comments within 30 days. Perrigo is now amending this application and responding to the Agency's comments in the February 23, 1996 correspondence. In addition, the Perrigo Company is respectfully requesting expedited review of this amendment. Please see the attached rational for expedited review as well as responses to all of the Agency's comments.

The Perrigo Company along with _____ would like to meet with the Agency to discuss and resolve any concerns in order to expedite review and approval of this application. Please contact me by telephone at (616) 673-7604 or by FAX at 616-673-7655.

Respectfully submitted,

Virginia K. Green

Virginia K. Green
Regulatory Affairs

enc.

xc: J. Eaton
D. Jespersen
E. Pileggi

1
151
4-26-96



NEW CORRESP

RECEIVED

NC

March 11, 1996

MAR 13 1996

Office of Generic Drugs, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Keith K. Chan, Ph.D.
Director, Div. of Bioequivalence

GENERIC DRUGS

RE: Miconazole Nitrate Vaginal Suppositories, 100 mg
ANDA 74-395

Dear Dr. Chan:

This letter is in response to the Agency's communication dated February 23, 1996. In that letter, the Agency commented on bioequivalence data submitted in ANDA 74-395, Miconazole Nitrate Vaginal Suppositories, 100 mg.

The Perrigo Company will respond to all comments raised by the Agency within 30 days. If you have any questions please feel free to contact me by telephone at (616) 673-7670 or by FAX at 616-673-7655.

Respectfully submitted,

Jacqueline M. Eaton
Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

16.027
151
4.26.96

3/7/96

To: Jim Harlick
(514) 333-0033
Phoenix Intl

FILE

From: Jason A. Gross
Project Manager
Division of Bioequivalence
Office of Generic Drugs
(301) 594-2290

RE: FDA letter dated 2/23/96
ANDA 74-395
L. Perrigo Co.
Miconazole Nitrate Vaginal Suppositories, 100 mg.
March 4, 1996, memo from Perrigo signed by Jacqueline
Eaton, granting the Agency permission to release
information to .

Dr. Harlick:

As we discussed; item #1 of the 2/23/96 letter specified the following:

The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo-group and 55 in the Ortho-group).

The 19 subjects the Agency deleted from the analysis are as follows:

Subject numbers: 22, 45, 47, 42, 122, 129, 134,
138, 152, 158, 163, 165, 24, 112,
141, 151, 160, 164, 168,

Thanks
JAG

S

3-7-96

ANDA 74-395

Food and Drug Administration
Rockville MD 20857

FEB 23 1996
DEFICIENCY LETTER

L. Perrigo Co.
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

Dear Madam:

This is in reference to your abbreviated new drug application for Miconazole Nitrate Vaginal Suppositories, 100 mg.

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

1. The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo-group and 55 in the Ortho-group). **evaluable*
2. The Agency only considered subjects for analysis who had resolution of all symptoms of disease at the second post-treatment visit (and subjects had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture at all visits to be therapeutic cures. Patients who were either a clinical failure and/or a mycological failure at either of the two follow-up visits were considered to be therapeutic failures. The following table summarizes the differences: *clinical failure*

Group	Visit 2		Visit 3	
	Agency [Perrigo]		Agency [Perrigo]	
<u>Mycological Cure Rate</u>				
Perrigo	51/56	[62/68]	40/56	[50/63]
Ortho	52/55	[58/62]	44/55	[48/60]

Clinical Cure Rate

Perrigo	55/56	[68/68]	47/56	[55/64]
Ortho	54/55	[61/62]	50/55	[56/60]

<u>Therapeutic Cure Rate</u>	<u>Visit 3</u>
	<u>Agency [Perrigo]</u>
Perrigo	40/56 [48/68]
Ortho	43/55 [47/62]

3. The Agency evaluated the data based on 111 evaluable subjects as summarized above and concluded that:

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

*n. analysis
didn't
meet
80-120%
CI*

- (4) 3. The summary report, IRB approval letter, drug composition statement, nor the product formulation data documented the product Lot number used in the study. The lot numbers, 2T6450 for the test and 22A125 for Ortho product were recorded only in the protocol. In future the Lot numbers of products used should be properly recorded on all forms.

document

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

Sincerely yours,

151

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

Redacted

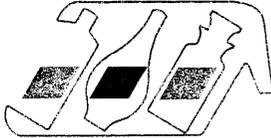
3

pages of trade secret and/or

confidential

commercial

information



PERRIGO COMPANY
FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

FILE

CONFIRMATION OF FAX

March 4, 1996
VIA FAX: 301-594-0181

Jason A. Gross, Pharm.D.
FDA, Office of Generic Drugs
Division of Bioequivalence
7500 Standish Place, HFD 612
Rockville, MD 20855

RE: 74-395 Miconazole 7-Day Suppository

Dear Dr. Gross:

This letter authorizes the FDA to release patient information records to _____
_____ for the above-referenced application.

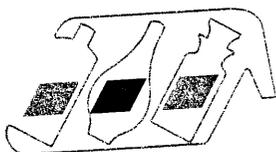
If you have any questions or need further information regarding this matter, please feel free to contact me at 616-673-7670 or fax 616-673-7655.

Respectfully,

Jacqueline M. Eaton
Regulatory Affairs Manager

cc: _____

Virginia Green



PERRIGO COMPANY
 FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

*Patel - AMU Weikel
 12/21/95*

December 14, 1995
 VIA FEDERAL EXPRESS

MINOR AMENDMENT
 ANDA 74-395

Office of Generic Drugs
 CDER, FDA, OPS
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773
 Attn: Rashmikant M. Patel

NDA ORIG AMENDMENT
 N/AM

RECEIVED

Re: Miconazole Nitrate Vaginal Suppository
 ANDA 74-395

DEC 18 1995

Dear Dr. Patel:

This Minor Amendment to ANDA 74-395, Miconazole Nitrate Vaginal Suppositories, is being filed in accordance with 21 CFR 314.120. This Minor Amendment responds to all deficiencies listed in the Agency's letter dated November 14, 1995 received November 15, 1995.

GENERIC DRUGS

The holder of DMF # _____ has notified Perrigo that they have responded to FDA's communication regarding deficiencies in their DMF. Attached is a copy of a letter from _____ confirming their response.

With respect to DMFs (also referred to under _____), held by _____, Perrigo requests these DMFs be withdrawn from ANDA 74-395 for the following reasons:

- DMFs for inactive ingredients contained in ANDA products are not required in the ANDA under the regulations.
- The listed drug NDA 18-520, referenced in Perrigo's ANDA 74-395, uses the same _____ materials from _____ as Perrigo. Since the listed drug was given approval to use these materials, in all fairness, Perrigo should also be given approval to use these materials. Supporting information from the Monistat 3 Vaginal Suppositories Summary Basis of Approval, a related product, was obtained via FOI:

"6. Components and Composition: Each 2.5 gram suppository contains 200mg of miconazole nitrate, _____ Drug is similar to NDA 18-520 except that it contains twice the amount of active ingredient. The 100mg were taken from the _____, however, the ratio of the _____ to each other remains the same."

2/1/95

In conclusion, the listed drug currently marketed under NDA 18-520 contains the same hydrogenated vegetable oils, from _____ as Perrigo's proposed drug product. Perrigo plans to manufacture the proposed drug product with the _____ but requests that the DMF references be removed from ANDA 74-395.

Further, please find enclosed Perrigo's revised final printed labeling for the container labels, carton labeling and patient package insert according to the changes described in the Agency's November 14, 1995 letter.

A copy of the executed field copy certification is also enclosed.

If you require further information please contact me at the address on this letter (attention: Jacqueline Eaton, Plant 6) or :

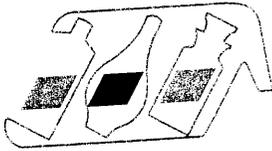
616-673-7670 (telephone)
616-673-7655 (fax)

Respectfully submitted,

J. M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL



PERRIGO COMPANY
FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

CERTIFICATION OF FIELD COPY

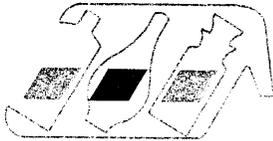
In accordance with 21 CFR 314.94(d)(5) I certify that a field copy which is a true copy of the MINOR AMENDMENT dated December 14, 1995 for Perrigo's Miconazole Nitrate Vaginal Suppository, ANDA 74-395, has been provided to the Detroit District Field Office of the Federal Food & Drug Administration at the following address:

Mr. John Dempster
Director, Compliance Branch
1560 Jefferson Avenue
Detroit, MI 48207

Jacqueline M. Eaton
Jacqueline M. Eaton
Regulatory Affairs Manager

December 14, 1995
Date

**APPEARS THIS WAY
ON ORIGINAL**



PERRIGO COMPANY

FROM LAB TO LABEL • QUALITY HEALTH AND BEAUTY PRODUCTS

November 29, 1995
VIA FACSIMILE

NEW CORRESP
NC

CONFIRMATION OF FAX

Noted
12/14/95
ISI

Ms. Anna Marie Wiekel, CSO
Office of Generic Drugs
FDA, CDER, OPS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **Miconazole Nitrate Vaginal Suppository**
ANDA 74-395

Dear Ms. Wiekel:

Perrigo acknowledges receipt of the Agency's Minor Deficiency letter dated November 14, 1995 for Miconazole Nitrate Vaginal Suppository, ANDA 74-395.

Perrigo is working on a Minor Amendment which will respond to the deficiency items described in the Agency's November 14, 1995 correspondence.

If you have any further questions, please contact me at:

616-673-7670 (telephone)
616-673-7655 (fax)

Respectfully submitted,

J. M. Eaton
Jacqueline M. Eaton
Regulatory Affairs Manager

xc: D. Jespersen, N. Wilmore

RECEIVED

DEC 05 1995

GENERIC DRUGS

14 Dec 95
ISI



74395

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service 21

Rockville MD 20857

Perrigo Company
Attention: David Jaspersen
117 Water Street
Allegan, Michigan 49010

NOV 22 1995

Reference Number: OGD 95-274

Dear Mr. Jaspersen:

This letter is in response to your October 11 and 12, 1995, request for a meeting with the Office of Generic Drugs (OGD) to discuss pending applications and general bioequivalence issues. Reference is also made to the phone conversation between yourself and Jason A. Gross, Pharm.D. on October 25, 1995.

The Office generally reserves meetings with firms to resolve complex scientific issues that cannot readily be responded to by written correspondence. Rather than granting your meeting request, the Office provides the remarks described below.

- A. In regards to filing an application, OGD has issued numerous industry letters and Policy and Procedure guides on these issues. To obtain a copy of these documents, please call the executive secretariat at (301) 594-1012. If you still have questions after reading these documents, contact Mr. Peter Rickman, in the Regulatory Support Branch, at (301) 594-0315, and/or Mr. Charlie Hoppes, in the Labeling Review Branch, at (301) 594-0365, for labeling questions.
- B. In regard to the bioequivalency issues related to Clemastine Fumarate Tablets, USP, abbreviated new drug application (ANDA) 74-512:
1. The Division of Bioequivalence has completed its review and has no further questions at this time.
 2. OGD notes that though it was acceptable at this point in time to conduct a multiple-dose study, Perrigo is advised that if *in vivo* bioequivalence testing is required to support changes, OGD may require that a single-dose study be conducted in preference to a multiple-dose study.
 3. The following dissolution testing will need to be incorporated into your stability and quality control programs:

7

The dissolution testing should be conducted in 500 ml pH 4.0 citrate buffer at 37°C using United States Pharmacopeia (USP) XXIII apparatus II (paddle) at 50 rpm. The test should meet the following specifications:

Not less than — of the labelled amount of the drug in the dosage form is dissolved in 30 minutes.

4. The bioequivalency comments expressed above, may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, 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.

C. Bioequivalence review status of Miconazole Nitrate Vaginal Suppositories, ANDA 74-395:

As discussed with Dr. Gross, and expressed in our previous correspondence of August 24, 1995, this application, submission date July 30, 1993, is under review by The Office of New Drug Evaluation (NDE). Once the review has been completed you will be notified by written correspondence. The Office acknowledges the long delay in the review this application. As Dr. Gross explained due to the nature of the study it must be reviewed by a Medical Review Officer (MRO). Currently, OGD must utilize the expertise of NDE.



E. Women in Bioequivalence Studies:

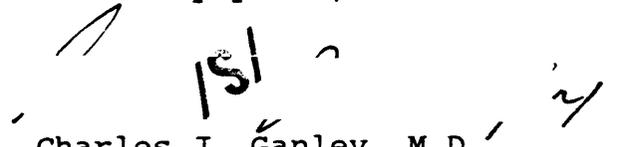
The Office does have a policy regarding the use of women in bioequivalence studies which states that gender should not be an exclusion criterion for general studies unless warranted for certain medications and/or safety reasons.

- F. Your questions concerning the SUPAC proposal and how it will relate to manufacturing site changes was recently discussed at the October 1995, National Association of Pharmaceutical Manufacturers (NAPM) workshop in Newark, New Jersey. As presented at the meeting, all SUPAC issues will be addressed to regulated industry through a Center for Drug Evaluation and Research (CDER) training program and a guidance to be published in the Federal Register. The Center is currently sharing the SUPAC proposal with its reviewers and will be expanding that to our field offices and then to the regulated industry. OGD is confident that your questions will be addressed during this process.

The guidance offered in this correspondence represents the best judgement OGD can offer based on the submitted information, current scientific knowledge, and the proposed issues at hand. Revisions of our statements may be necessary as scientific knowledge progresses and information changes.

If you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,


Charles J. Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research



Memorandum

. DEC 20 1994

Date

From Branch Chief, Investigations &
Compliance Evaluation Branch, HFD-324

Subject Recommendation to Withhold Approval
ANDA 74-395, Miconazole Nitrate Vaginal
Suppositories, 100 mg.

Appl: Perrigo Co.
Allegan, MI

To Gordon R. Johnston, HFD-632
Regulatory Support Staff

Manuf: Perrigo Co.
North Labs Div
Montague, MI
CF #91823985

We have completed our review of the pre-approval inspection report for Perrigo Company which covered the listed application. The inspection was performed in January 24-31, 1994, and resulted in the district's recommendation that approval of the application be withheld. Division of Manufacturing and Product Quality, DMPQ concurs with the district's recommendation to withhold approval.

The inspection noted problems including, but not limited to the following:

1. The firm's production processes revealed numerous GMP deficiencies. For example:

k

3

Accordingly, we are providing one copy of the EIR and exhibits. If you have any questions please contact CSO Brenda L. Holmes or the undersigned at 301/827-0061.

1st
Mark A. Lynch

Attachment

APPEARS THIS WAY
ON ORIGINAL

11
J. Phillips

ANDA 74-395

FEB 23 1996

L. Perrigo Co.
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

Dear Madam:

This is in reference to your abbreviated new drug application for Miconazole Nitrate Vaginal Suppositories, 100 mg.

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

1. The submission specified that there was a total of 130 evaluable subjects (68 in the Perrigo-group and 62 in the Ortho-group). The Agency reviewed the data associated with these subjects and concluded that of the 130 subjects evaluated by Perrigo, 19 subjects failed to return within acceptable time frames for evaluation at visits 2 or 3 and thus, are not evaluable. Based on Agency analysis of the study there are 111 evaluable subjects, (56 in the Perrigo-group and 55 in the Ortho-group).
2. The Agency only considered subjects for analysis who had resolution of all symptoms of disease at the second post-treatment visit (and subjects had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture at all visits to be therapeutic cures. Patients who were either a clinical failure and/or a mycological failure at either of the two follow-up visits were considered to be therapeutic failures. The following table summarizes the differences:

Group	Visit 2		Visit 3	
	Agency [Perrigo]		Agency [Perrigo]	
<u>Mycological Cure Rate</u>				
Perrigo	51/56	[62/68]	40/56	[50/63]
Ortho	52/55	[58/62]	44/55	[48/60]

Clinical Cure Rate

Perrigo	55/56	[68/68]	47/56	[55/64]
Ortho	54/55	[61/62]	50/55	[56/60]

<u>Therapeutic Cure Rate</u>	<u>Visit 3</u>
	<u>Agency [Perrigo]</u>
Perrigo	40/56 [48/68]
Ortho	43/55 [47/62]

3. The Agency evaluated the data based on 111 evaluable subjects as summarized above and concluded that:
 - a. The visit 3 data for "mycologic cure rates" fails to support the claim of equivalency due to failure to meet the lower bound of the 80-120% confidence interval.
 - b. The visit 3 data for "therapeutic cure rate" fails to support the claim of equivalency due to failure to meet the 80-120% confidence interval.

3. The summary report, IRB approval letter, drug composition statement, nor the product formulation data documented the product Lot number used in the study. The lot numbers, 2T6450 for the test and 22A125 for Ortho product were recorded only in the protocol. In future the Lot numbers of products used should be properly recorded on all forms.

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

Sincerely yours,


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

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



DATE: 11.15.95

TO: L. Perrigo Co.

FROM: A. M. Weibel

Attn: Jackie Eaton

CSO

PHONE: (616) 673-~~7670~~ 7670

PHONE: (301) 594-1841

FAX: (616) 673-7655

FAX: (301) 594-0180

NUMBER OF PAGES: 2
(Excluding Cover Sheet)

With this facsimile, the Office of Generic Drugs is providing you with a copy of a not approvable letter requesting your response in the form of a **MINOR AMENDMENT** for the following abbreviated new drug/antibiotic application:

ANDA/AADA NUMBER: 74-395 DATE OF LETTER: 11.13.95

NAME OF DRUG PRODUCT: Miconazole Nitrate (Vaginal Suppositories)

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.



ANDA 74-395

Food and Drug Administration
Rockville MD 20857

L. Perrigo Co.
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

NOV 14 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated July 30, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendments dated November 15, 1994 and December 15, 1994.

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

Chemistry Deficiency

_____ Holders of DMF # _____ and DMF #'s _____, have been notified of current deficiencies in their Drug Master Files. Please do not respond to this communication until you receive notice from the DMF holders that they have responded to our communication to them.

Labeling Deficiencies

Container:

Revise to read, "...Suppository...", (singular).

Carton:

1. We acknowledge your comments regarding the tamper resistant packaging for your product.
2. Delete the word, " _____ " from your storage recommendations, e.g., "Store at room...".
3. Increase the print quality of your final printed labeling.

Patient Package Insert:

1. Please submit final printed patient package insert labeling which is printed on both sides.
2. See comment 2. under Carton.
3. WHAT ARE VAGINAL...

In paragraph three, delete _____ where it precedes "vaginal yeast infections", (two places).

4. WARNINGS

Delete the word " _____ " in the first sentence.

Please revise your container labels, carton labeling, and patient package insert, then prepare and submit final printed labeling.

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 bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RS

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

ORIG.



PERRIGO COMPANY
FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

December 15, 1994
VIA FEDERAL EXPRESS

**FOLLOW-UP TO
MINOR AMENDMENT**

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Rashmikant M. Patel, Ph.D.
Director, Division of Chem I

NDA ORIG AMENDMENT
N/A/M

Re: **Miconazole Suppository - ANDA 74-395**

Dear Dr. Patel:

As indicated in Perrigo's MINOR amendment filed November 15, 1994 to ANDA 74-395, please find enclosed follow-up information with respect to Chemistry Amendment A.4.

As stated in the MINOR deficiency letter issued October 28, 1994, Chemistry Deficiency A.4. states:

Please add a _____ as a release test and, include the _____ and average suppository weight in your amended finished product assay report.

The _____ as a release test and the average suppository weight have been added to the attached finished product assay report. The melting range limits were also tightened as indicated in response No. 6 of the MINOR amendment.

A copy of the attached revised assay procedure no. 1340.5 includes a section for performing the _____

Also, a mathematical error was noted while performing an additional review of the residual solvent test results presented in our response to Chemistry Deficiency A.3. The correct results are attached.

Please contact me directly if you have any further questions.

Respectfully submitted,
J. M. Eaton
Jacqueline M. Eaton
Regulatory Affairs Manager

RECEIVED

DEC 19 1994

GENERIC DRUGS

J. M. Eaton

ANDA 74-395

L. Perrigo Co.
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

NOV 14 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated July 30, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendments dated November 15, 1994 and December 15, 1994.

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

Chemistry Deficiency

_____ Holders of DMF # _____ and DMF #'s _____ have been notified of current deficiencies in their Drug Master Files. Please do not respond to this communication until you receive notice from the DMF holders that they have responded to our communication to them.

Labeling Deficiencies

Container:

Revise to read, "...Suppository...", (singular).

Carton:

1. We acknowledge your comments regarding the tamper resistant packaging for your product.
2. Delete the word, _____, from your storage recommendations, e.g., "Store at room...".
3. Increase the print quality of your final printed labeling.

Patient Package Insert:

1. Please submit final printed patient package insert labeling which is printed on both sides.
2. See comment 2. under Carton.
3. WHAT ARE VAGINAL...

In paragraph three, delete _____ where it precedes "vaginal yeast infections", (two places).

4. WARNINGS

Delete the word "recurrent" in the first sentence.

Please revise your container labels, carton labeling, and patient package insert, then prepare and submit final printed labeling.

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 bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RS

11/13/95

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



PERRIGO COMPANY
FROM LAB TO LABEL · QUALITY HEALTH AND BEAUTY PRODUCTS

Labony Review 12/2/94
ISI

NOTED
11/23/94
ISI

November 15, 1994
VIA FEDERAL EXPRESS

AMENDMENT *FPU*
4/27/94

MINOR AMENDMENT

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Rashmikan M. Patel, Ph.D.
Director, Division of Chem I

Re: **Miconazole Suppository**
ANDA 74-395

Dear Dr. Patel:

This Minor amendment to ANDA 74-395, Miconazole Nitrate Vaginal Suppositories, is being filed in accordance with 21 CFR 314.120.

This Minor Amendment responds to all deficiencies listed in the Agency's letter dated October 28, 1994. Each deficiency and Perrigo's response is attached.

Perrigo thanks the Agency for their participation in a conference call November 3 to clarify issues raised in the October 28, 1994 correspondence.

Should you require additional information, please contact me directly at phone no. 616-673-7670, fax no. 616-673-7664 or the address on this letterhead.

Respectfully submitted,

J. M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

xc: Elizabeth Pileggi, V.P. Technical Affairs
Carl Johnson, V.P. Pharmaceutical Business Development

RECEIVED

NOV 16 1994

GENERIC DRUGS

MINOR Amendment
ANDA 74-395
November 15, 1994

A. Chemistry Deficiencies

1. Before you can reduce testing of hydrogenated vegetable oil (as _____, you should have previously established a vendors validation program with the respective suppliers. Please support your abbreviated testing or perform all tests as defined by the USP XXII/NFXVII, 5th supplement, p. 2747. Tests for _____ method II <231> _____ value <401> _____ matter <401>, _____ value method II <401>, and _____ /LOD <731> for hydrogenated vegetable oil should be done.

RESPONSE: The tests for _____ Method II, _____ value, _____ matter, _____ Value Method II, and _____ have been added to our specifications for Hydrogenated Vegetable Oil (as _____). A copy of the updated specifications are attached.

APPEARS THIS WAY
ON ORIGINAL

L. Perrigo Co.
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

OCT 28 1994

Dear Madam:

This is in reference to your abbreviated new drug application dated July 30, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

Reference is also made to your amendment dated March 8, 1994.

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

A. Chemistry Deficiencies

p. 6 1.

[Redacted]

p. 8 2.

Please include on your COA the known residual solvents that are specified on the drug substance suppliers' C.O.A.'s

p. 5 3.

Please submit SOP 614-40 and the resultant method validation study data concerning residual solvents.

p. 8 4

[Redacted]

p. 1 5.

You are reminded to perform room temperature stability data on future lots of product at the

appropriate test stations (3, 6, 9, 12, 18 and 24 months, and yearly thereafter until the desired expiration date is reached). Reduction of the testing requirements should be supplemented after sufficient data has been accumulated.

6. Please revise the finished product specifications to include a more narrow melting range specification.

7. The holder of DMF # _____ for the drug substance, and of DMF's _____ for _____ have been notified of deficiencies in their Drug Master Files.

B. LABELING DEFICIENCIES

General:

Revise the established name of your product on all labels and labeling as follows: Miconazole Nitrate Vaginal Suppositories USP, 100 mg

Container:

See general comment above (relocate the comma).

Carton:

1. The innovator utilizes a printed seal for both end flaps of the carton. You have directed the consumer to inspect the plastic unit for signs of tampering. Although only one tamper resistant feature is required by 21 CFR 211.132, we would encourage you to consider a similar design as the listed drug.
2. See general comment above

Insert:

1. Please revise the established name of your product in the title of the insert as requested in the general comment above.
2. In the section "WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?":

Italicize "*Candida*" where it appears.

3. We acknowledge that we had requested that the entire "ADVERSE REACTIONS (SIDE EFFECTS)" section be deleted. Based on the listed

drug's most current approved labeling, however, we request that you add this section back into your package insert as it appeared in your July 30, 1993, submission.

4. After the "FOR BEST RESULTS" section, add a new section as follows:

IF YOU HAVE A QUESTION

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

Please revise your container labels, carton labeling, and patient package insert, then prepare and submit final printed labeling or draft labeling if you prefer.

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

Sincerely yours,

J Rashmikan¹⁵¹ M. Patel, Ph.D. 12/2/94
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research



FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

Original

NDA ORIG AMENDMENT

Dr. Labeled

AC

March 8, 1994
VIA FEDERAL EXPRESS

Rashmikant M. Patel, Ph.D.
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA 74-395**
MAJOR AMENDMENT

Dear Dr. Patel:

This Major Amendment to ANDA 74-395, Miconazole Nitrate Vaginal Suppositories, is being filed in accordance with 21 CFR 314.120.

This Major Amendment responds to all deficiencies listed in the Agency's letter dated February 16, 1994, received by Perrigo on February 22, 1994. Each deficiency and Perrigo's response is attached.

Respectfully submitted,

J. M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

xc: Elizabeth Pileggi, V.P. Technical Affairs
Carl Johnson, V.P. Pharmaceutical Business Development

[RECEIVED]

MAR 9 1994

GENERIC DRUGS

14 Mar 94
ISI

FEB 16 1994

L. Perrigo Co.
Attention: Michael B. Shubeck
117 Water Street
Allegan, MI 49010

Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Suppositories USP, 100 mg.

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

A. Chemistry Deficiencies

1. _____

2. _____

3. _____

4. _____

6.

7.

1

B. Labeling Deficiencies

We encourage the inclusion of USP in the established name of this product, on all labels and labeling.

Container: Not Satisfactory (Drug Film)

Include the strength (100 mg).

Carton: Not Satisfactory

1. Front Panel

c. Delete sentence: " ~~_____~~ ✓

5. **CONTENTS**

"...100 mg of miconazole..." ✓

6. **DIRECTIONS FOR USE**

Under "3" : "As shown in the pictures, ✓
this..."

7. **ADVERSE REACTIONS (SIDE EFFECTS)** ✓

Delete entire section.

8. **FOR BEST RESULTS**

"...bowel movement or urination." ✓

Please revise your labels and labeling, then prepare and submit draft labels and labeling.

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

- A. Please be reminded that the Miconazole Nitrate Vaginal Suppository is a USP product and must pass all USP compendial testing for that product. The USP regulatory method takes precedence in resolving any disputes or contentions concerning product quality.
- B. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.
- C. Please submit a certified statement which declares the firm in compliance with all the local state and federal environmental regulations relative to holding and processing all materials used in the manufacture of Miconazole Nitrate Suppository.

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. You will be notified in a

separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

2/11/94
Y Rashmikant M. Patel, Ph.D
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-395
ANDA #74-395/DUP/Division file
Field Copy
HFD-600/Reading file

Endorsements:

HFD-629/L.Fulton/1-31-94 *IS/ 2-4-94*
HFD-613/C.Hoppes/2-3-94 *IS/ 2/4/94*
HFD-619/P.Schwartz, Ph.D./1-31-94 *IS/ 2/4/94*
HFD-629/J.Dawson/CSO/2-2-94 *IS/ -4-94*
X:\Wpfile\Majors\Fulton\74395OLr.LLF
F/T by MM 2-3-94
Deficiency letter - Major Amendment

ANDA 74-395

AUG 24 1993

L. Perrigo Company
Attention: Michael B. Shubeck
117 Water Street
Allegan, MI 49010

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

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

DATE OF APPLICATION: July 30, 1993

DATE OF RECEIPT: August 4, 1993

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

Handwritten signature: [unclear] 8/24/93

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

cc: ANDA #74-395
DUP/Division File
HFD-600/Reading File
HFC-130/JAllen
HFD-320/Hamilton
HFD-650/~~MB~~
HFD-82
HFD-632/MBennett
HFD-634/PSchwar
R/D initialed by WRusse and GJohnston
bcw/8-20-93/74395ack.ltr
F/T by bcw/8-23-93
acknowledgment letter

Handwritten notes and stamps:
8-23-93
12/93
ISI
8/23/93
ISI
8/23/93



PERRIGO COMPANY
FROM LAB TO LABEL • QUALITY HEALTH AND BEAUTY PRODUCTS

505(j)(2)(A)
ok to file
WS not
8/10/93
WMM
8/16/93

July 30, 1993

Dr. Roger L. Williams, M.D., Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

AUG 0 4 1993

Re: **Miconazole Nitrate Vaginal Suppository**
Abbreviated New Drug Application

GENERIC DRUGS

Dear Dr. Williams:

The L. Perrigo company is submitting for your review and approval, our ANDA for Miconazole Nitrate Vaginal Suppositories pursuant to 505(j) of the Federal Food, Drug, Cosmetic Act. Miconazole Nitrate Vaginal Suppositories (miconazole nitrate 100mg) are identical in strength, indications, active ingredient, inactive ingredient, route of administration and dosage form to R.W. Johnson's Monistat® 7 Suppositories (miconazole nitrate 100mg).

Monistat® 7 Suppositories (NDA 18-520, supplement 002) are listed in the Thirteenth Edition of Approved Drug Products with Therapeutic Equivalence Evaluations as an OTC drug with no patent protection or market exclusivity.

We are requesting an initial 2 year expiration date for Miconazole Nitrate Vaginal Suppositories, based on 3 months of accelerated stability testing results.

For the reviewer's convenience, an extra set of Drug Master File referral letters is included in Section 20 of this application.

Should you require additional information, please contact me at 616-673-7670.

Sincerely,

Jacqueline M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager