CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-760

Generic Name: Miconazole Nitrate Vaginal Cream, 2%

Sponsor: L. Perrigo Company

Approval Date: May 15, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74-760
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

APPROVAL LETTER

MAY 15 1997

ANDA 74-760

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

Dear Mr. Jespersen:

This refers to your abbreviated new drug application dated September 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Cream, 2%.

Reference is also made to your amendments dated March 20, August 9, October 1, 4, 16 and 29, 1996, and April 15, 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 Cream, 2% to be bioequivalent to the list drug, Monistat® 7 of RW Johnson Pharmaceutical Research Institute.

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

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

Sincerely yours,

/S/ 5/15/97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

Final Printed Labeling

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Disposable Applicator-Front)

APPROVED EDUCATIONAL BROCHURE MAY 15 1997

CURES MOST VAGINAL YEAST INFECTIONS

MICONAZOLE NITRATE VAGINAL CREAM, 2%

RELIEVES EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION

INDICATIONS:

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

If you have any or all of the symptoms of a vaginal yeast infection (vaginal itching, burning, discharge) and if at some time in the past your doctor has told you that these symptoms are due to a vaginal yeast infection, then MICONAZOLE NITRATE VAGINAL CREAM should work for you. If, however, you have never had these symptoms before, you should see your doctor before using MICONAZOLE NITRATE VAGINAL CREAM. **MICONAZOLE NITRATE VAGINAL CREAM IS FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS AND FOR THE RELIEF OF EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION. IT DOES NOT TREAT OTHER INFECTIONS OR EXTERNAL ITCHING AND IRRITATION DUE TO CAUSES OTHER THAN YEAST INFECTIONS. IT DOES NOT PREVENT PREGNANCY.**

WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?

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

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

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV—the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you may have been exposed to HIV and are experiencing either frequently recurring vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

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

SYMPTOMS OF VAGINAL YEAST INFECTIONS

There are many signs and symptoms of a vaginal yeast infection. They can include:

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

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

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast and in relieving vulvar itching and irritation associated with a yeast infection. Do not use in eyes or take by mouth.
- **DO NOT USE MICONAZOLE NITRATE VAGINAL CREAM IF YOU HAVE ANY OF THE FOLLOWING SIGNS AND SYMPTOMS. ALSO, IF THEY OCCUR WHILE USING MICONAZOLE NITRATE VAGINAL CREAM, 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 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.
- Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using MICONAZOLE NITRATE VAGINAL CREAM.
- 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

One tube of vaginal cream containing miconazole nitrate 2%. Seven disposable applicators.

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Disposable Applicator-Back)

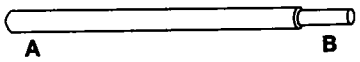
IMPORTANT: THE TUBE OPENING IS SEALED FOR YOUR PROTECTION. DO NOT USE IF THE TUBE SEAL HAS A HOLE IN IT OR IF THE SEAL CANNOT BE SEEN. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

DIRECTIONS FOR USE

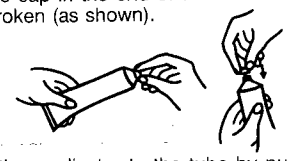
Vaginal Application

Begin treatment at bedtime. Before going to bed:

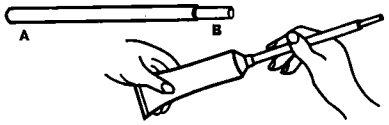
1 The first time you use a disposable applicator, pull the two pieces apart to see where the arrow is that indicates a full applicator. After locating the arrow, and before filling the applicator, push plunger "B" completely back inside "A". (Do not be concerned if the two come apart, they may easily be put back together.) See illustration.



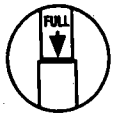
2 To open the tube, unscrew the cap. Turn the cap upside down and place the cap in the end of the tube. Push down firmly until the seal is broken (as shown).

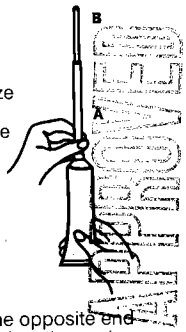


3 Attach the applicator to the tube by pushing end "A" of the applicator over the neck of opened tube. Turn applicator, pushing down until applicator is firmly on the neck of the tube (as shown).



4 Hold applicator firmly on the tube neck. Squeeze the tube from the bottom. This will force the cream into the applicator. Do this until the inside portion of the applicator plunger "B" is pushed out to the tip of the "FULL" arrow or the beginning of the green band. Separate applicator from tube. (See illustration)





5 Hold the applicator containing the cream by the opposite end from where the cream 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 cream 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 cream. This will reduce leakage.

You may want to use deodorant-free minipads or pantyshields during the time that you are using MICONAZOLE NITRATE VAGINAL CREAM. This is because the cream can leak and/or you may see some discharge. DO NOT USE TAMPONS.

6 After each use, replace cap and roll tube from bottom (as shown).

7 Throw away the applicator after each use. DO NOT FLUSH IN TOILET. Use a new applicator for each dose.

8 Repeat steps 3 through 7 before going to bed on each of the next six evenings.

External Vulvar Application

If needed, use the cream twice daily as follows:

1. Squeeze a small amount of cream on to your finger.
2. Gently apply the cream onto the skin (vulva) that itches and is irritated.
3. Repeat steps 1 and 2 each morning and evening as needed.

ADVERSE REACTIONS (SIDE EFFECTS)

The following side effects have been reported with the use of MICONAZOLE NITRATE VAGINAL CREAM: a temporary increase in burning, itching, and/or irritation when the cream is inserted. Abdominal cramping, headaches, hives, and skin rash have also been reported. If any of these occur, stop using MICONAZOLE NITRATE VAGINAL CREAM and consult your doctor.

FOR BEST RESULTS

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

IF YOU HAVE A QUESTION

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

ACTIVE INGREDIENT

miconazole nitrate 2% (100 mg per dose)

STORAGE

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

Manufactured by:
Perrigo Co.
Allegan MI, 49010, U.S.A.

07/96
496053

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Reusable Applicator-Front)

MAY 15 1997 *EDUCATIONAL BROCHURE* APPROVED

CURES MOST VAGINAL YEAST INFECTIONS

MICONAZOLE NITRATE VAGINAL CREAM, 2%

RELIEVES EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION

INDICATIONS:

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

If you have any or all of the symptoms of a vaginal yeast infection (vaginal itching, burning, discharge) and if at sometime in the past your doctor has told you that these symptoms are due to a vaginal yeast infection, then MICONAZOLE NITRATE VAGINAL CREAM should work for you. If, however, you have never had these symptoms before, you should see your doctor before using MICONAZOLE NITRATE VAGINAL CREAM. **MICONAZOLE NITRATE VAGINAL CREAM IS FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS AND FOR THE RELIEF OF EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION. IT DOES NOT TREAT OTHER INFECTIONS OR EXTERNAL ITCHING AND IRRITATION DUE TO CAUSES OTHER THAN YEAST INFECTIONS. IT DOES NOT PREVENT PREGNANCY.**

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

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV - the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you may have been exposed to HIV and are experiencing either frequently recurring vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

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SYMPTOMS OF VAGINAL YEAST INFECTIONS

There are many signs and symptoms of a vaginal yeast infection. They can include:

- Vaginal itching (ranging from mild to intense);
- A clumpy, vaginal discharge that may look like cottage cheese;
- Vaginal soreness, irritation, or burning, especially during vaginal intercourse;
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NOTE: Vaginal discharge that is different from above, for example, a yellow/green discharge or a discharge that smells "fishy", may indicate that you have something other than a yeast infection. If this is the case, you should consult your doctor before using MICONAZOLE NITRATE VAGINAL CREAM.

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast and in relieving vulvar itching and irriation associated with a yeast infection. Do not use in eyes or take by mouth.
- **Do not use MICONAZOLE NITRATE VAGINAL CREAM if you have any of the following signs and symptoms. Also, if they occur while you are using MICONAZOLE NITRATE VAGINAL CREAM, 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 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.
- Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using MICONAZOLE NITRATE VAGINAL CREAM.
- 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

One tube of vaginal cream containing miconazole nitrate 2%. One plastic applicator.

IMPORTANT: THE TUBE OPENING IS SEALED FOR YOUR PROTECTION. DO NOT USE IF THE TUBE SEAL HAS A HOLE IN IT OR IF THE SEAL CANNOT BE SEEN. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Reusable Applicator-Back)

APPROVED

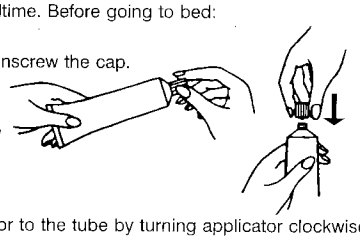
MAY 15

DIRECTIONS FOR USE

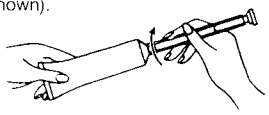
Vaginal Application

Begin treatment at bedtime. Before going to bed:

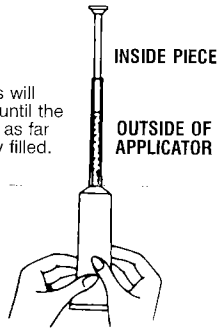
1 To open the tube, unscrew the cap. Turn the cap upside down and place the cap on the end of the tube. Push down firmly until the seal is broken (as shown).



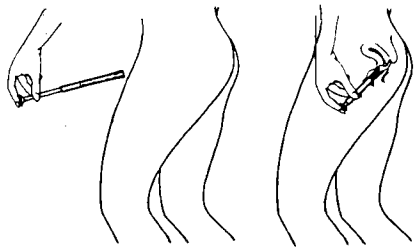
2 Attach the applicator to the tube by turning applicator clockwise (as shown).



3 Squeeze the tube from the bottom. This will force the cream into the applicator. Do this until the inside piece of the applicator is pushed out as far as it will go and the applicator is completely filled. Separate applicator from tube.



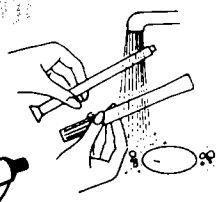
4 Hold the applicator containing the cream by the opposite end from where the cream is. Gently insert the applicator into the vagina as far as it will go comfortably.



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 cream 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 cream. This will reduce leakage.

You may want to use deodorant-free minipads or pantyshields during the time that you are using MICONAZOLE NITRATE VAGINAL CREAM. This is because the cream can leak and/or you may see some discharge. DO NOT USE TAMPONS.

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



6 After each use, replace cap and roll tube from bottom (as shown).

7 Repeat steps 2 through 6 before going to bed on each of the next six evenings.

External Vulvar Application

If needed, use the cream twice daily as follows:

1. Squeeze a small amount of cream onto your finger.
2. Gently apply the cream onto the skin (vulva) that itches and is irritated.
3. Repeat steps 1 and 2 each morning and evening as needed.

ADVERSE REACTIONS (SIDE EFFECTS)

The following side effects have been reported with the use of MICONAZOLE NITRATE VAGINAL CREAM: a temporary increase in burning, itching, and/or irritation when the cream is inserted. Abdominal cramping, headaches, hives, and skin rash have also been reported. If any of these occur, stop using MICONAZOLE NITRATE VAGINAL CREAM and consult your doctor.

FOR BEST RESULTS

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

IF YOU HAVE A QUESTION

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

ACTIVE INGREDIENT

miconazole nitrate 2% (100 mg per dose)

STORAGE

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

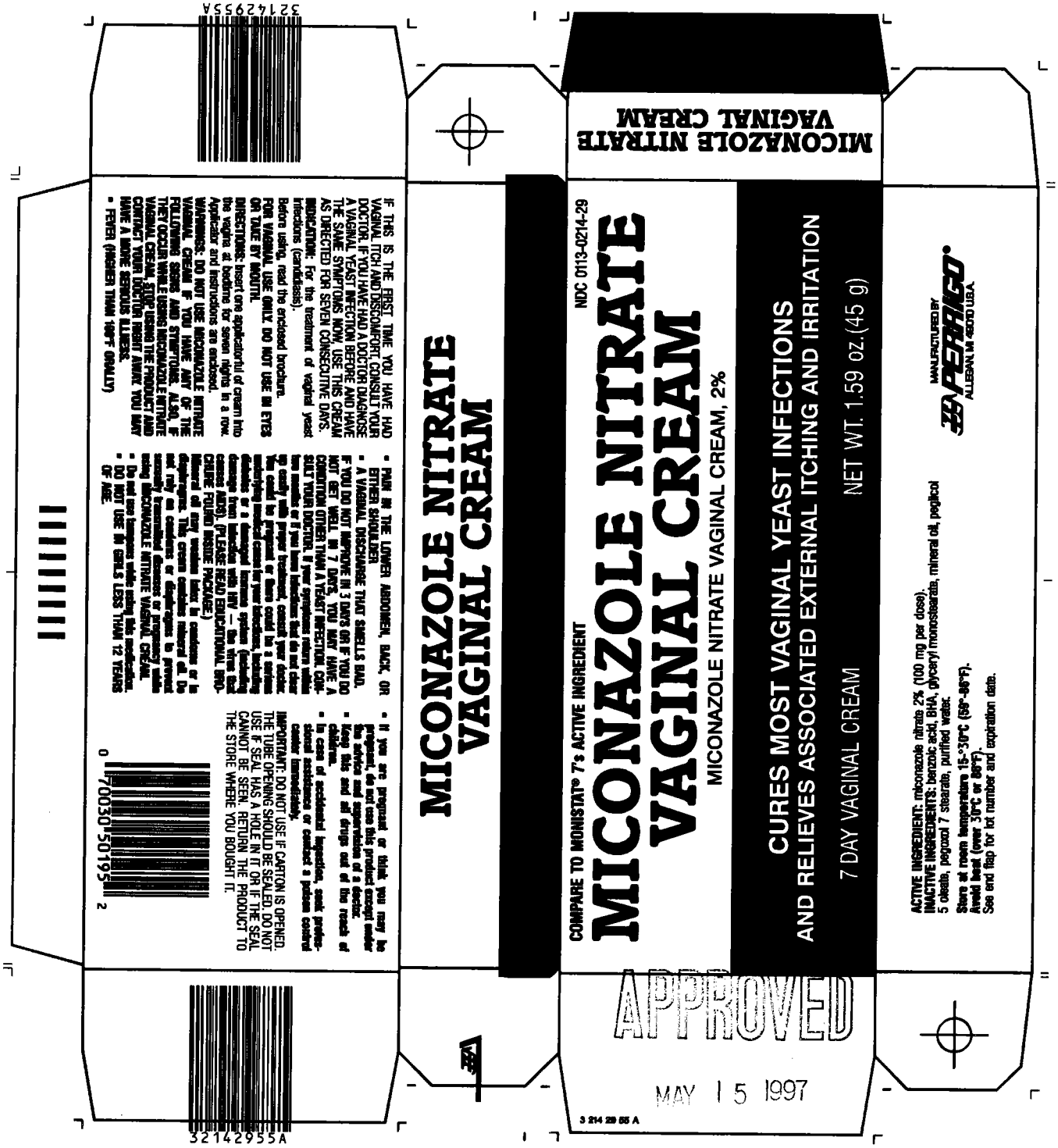
MANUFACTURED BY:
PERRIGO Co.
ALLEGAN, MI 49010, U.S.A.

07/96

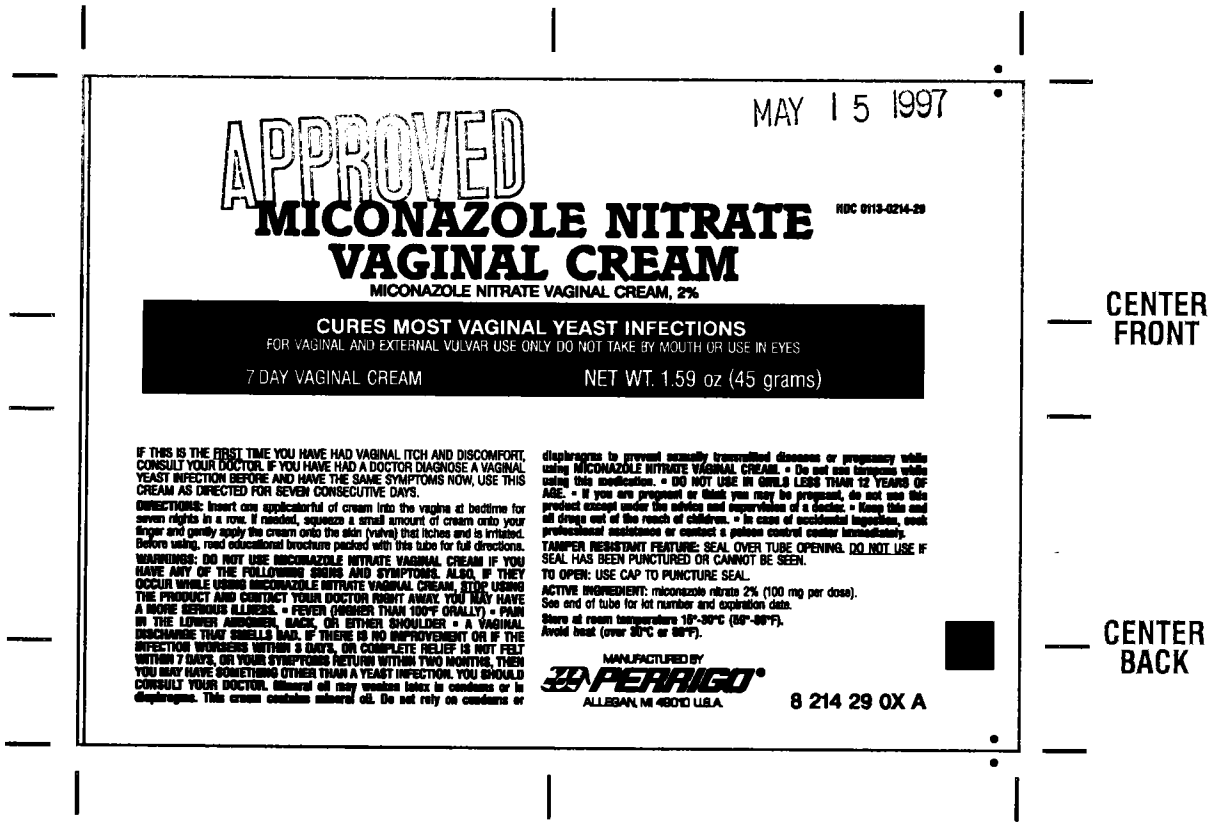
496062

Final Printed Labeling
ANDA 74-760
Carton - Disposable Applicator

Final Printed Labeling
ANDA 74-760
Carton - Reusable Applicator



Final Printed Labeling
ANDA 74-760
45 Gram Tube



APPROVED
MAY 15 1997

MICONAZOLE NITRATE VAGINAL CREAM

NDC 0113-0214-29

MICONAZOLE NITRATE VAGINAL CREAM, 2%

CURES MOST VAGINAL YEAST INFECTIONS
FOR VAGINAL AND EXTERNAL VULVAR USE ONLY DO NOT TAKE BY MOUTH OR USE IN EYES

7 DAY VAGINAL CREAM NET WT. 1.59 oz (45 grams)

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 THIS CREAM AS DIRECTED FOR SEVEN CONSECUTIVE DAYS.

DIRECTIONS: Insert one applicatorful of cream into the vagina at bedtime for seven nights in a row. If needed, squeeze a small amount of cream onto your finger and gently apply the cream onto the skin (vulva) that itches and is irritated. Before using, read educational brochure packed with this tube for full directions.

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

TAMPER RESISTANT FEATURE: SEAL OVER TUBE OPENING. DO NOT USE IF SEAL HAS BEEN PUNCTURED OR CANNOT BE SEEN.

TO OPEN: USE CAP TO PUNCTURE SEAL.

ACTIVE INGREDIENT: miconazole nitrate 2% (100 mg per dose).
See end of tube for lot number and expiration date.

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

MANUFACTURED BY
PERRIGO
ALLEGAN, MI 49010 U.S.A.

8 214 29 0X A

CENTER FRONT

CENTER BACK

ON 91-91

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Reusable Applicator-Front)

MAY 15 1991 EDUCATIONAL BROCHURE APPROVED

CURES MOST VAGINAL YEAST INFECTIONS

MICONAZOLE NITRATE VAGINAL CREAM, 2%

RELIEVES EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION

INDICATIONS:

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

If you have any or all of the symptoms of a vaginal yeast infection (vaginal itching, burning, discharge) and if at sometime in the past your doctor has told you that these symptoms are due to a vaginal yeast infection, then MICONAZOLE NITRATE VAGINAL CREAM should work for you. If, however, you have never had these symptoms before, you should see your doctor before using MICONAZOLE NITRATE VAGINAL CREAM. **MICONAZOLE NITRATE VAGINAL CREAM IS FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS AND FOR THE RELIEF OF EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION. IT DOES NOT TREAT OTHER INFECTIONS OR EXTERNAL ITCHING AND IRRITATION DUE TO CAUSES OTHER THAN YEAST INFECTIONS. IT DOES NOT PREVENT PREGNANCY.**

WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?

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

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

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV - the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you may have been exposed to HIV and are experiencing either frequently recurring vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

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

SYMPTOMS OF VAGINAL YEAST INFECTIONS

There are many signs and symptoms of a vaginal yeast infection. They can include:

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

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

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast and in relieving vulvar itching and irriation associated with a yeast infection. Do not use in eyes or take by mouth.
- **Do not use MICONAZOLE NITRATE VAGINAL CREAM if you have any of the following signs and symptoms. Also, if they occur while you are using MICONAZOLE NITRATE VAGINAL CREAM, 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 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.
- Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using MICONAZOLE NITRATE VAGINAL CREAM.
- 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

One tube of vaginal cream containing miconazole nitrate 2%. One plastic applicator.

IMPORTANT: THE TUBE OPENING IS SEALED FOR YOUR PROTECTION. DO NOT USE IF THE TUBE SEAL HAS A HOLE IN IT OR IF THE SEAL CANNOT BE SEEN. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Reusable Applicator-Back)

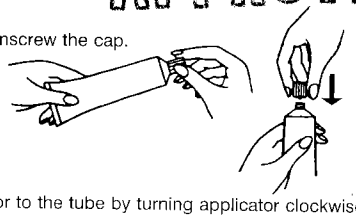
APPROVED MAY 15 [illegible]

DIRECTIONS FOR USE

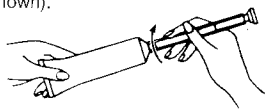
Vaginal Application

Begin treatment at bedtime. Before going to bed:

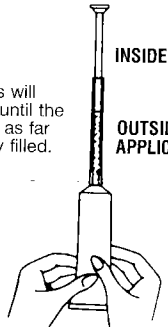
1 To open the tube, unscrew the cap. Turn the cap upside down and place the cap on the end of the tube. Push down firmly until the seal is broken (as shown).



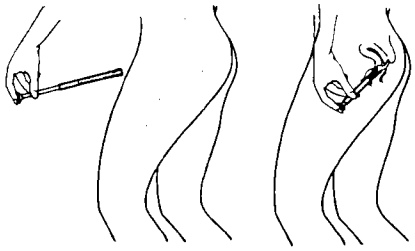
2 Attach the applicator to the tube by turning applicator clockwise (as shown).



3 Squeeze the tube from the bottom. This will force the cream into the applicator. Do this until the inside piece of the applicator is pushed out as far as it will go and the applicator is completely filled. Separate applicator from tube.



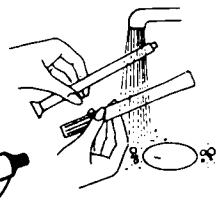
4 Hold the applicator containing the cream by the opposite end from where the cream is. Gently insert the applicator into the vagina as far as it will go comfortably.



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 cream 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 cream. This will reduce leakage.

You may want to use deodorant-free minipads or pantyshields during the time that you are using MICONAZOLE NITRATE VAGINAL CREAM. This is because the cream can leak and/or you may see some discharge. DO NOT USE TAMPONS.

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



6 After each use, replace cap and roll tube from bottom (as shown).

7 Repeat steps 2 through 6 before going to bed on each of the next six evenings.

External Vulvar Application

If needed, use the cream twice daily as follows:

1. Squeeze a small amount of cream onto your finger.
2. Gently apply the cream onto the skin (vulva) that itches and is irritated.
3. Repeat steps 1 and 2 each morning and evening as needed.

ADVERSE REACTIONS (SIDE EFFECTS)

The following side effects have been reported with the use of MICONAZOLE NITRATE VAGINAL CREAM: a temporary increase in burning, itching, and/or irritation when the cream is inserted. Abdominal cramping, headaches, hives, and skin rash have also been reported. If any of these occur, stop using MICONAZOLE NITRATE VAGINAL CREAM and consult your doctor.

FOR BEST RESULTS

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

IF YOU HAVE A QUESTION

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

ACTIVE INGREDIENT

miconazole nitrate 2% (100 mg per dose)

STORAGE

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

MANUFACTURED BY:
PERRIGO Co.
ALLEGAN, MI 49010, U.S.A.

07/96

496062

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Disposable Applicator-Front)

APPROVED MAY 15 1997

EDUCATIONAL BROCHURE

CURES MOST VAGINAL YEAST INFECTIONS

MICONAZOLE NITRATE VAGINAL CREAM, 2%

RELIEVES EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION

INDICATIONS:

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

If you have any or all of the symptoms of a vaginal yeast infection (vaginal itching, burning, discharge) and if at some time in the past your doctor has told you that these symptoms are due to a vaginal yeast infection, then MICONAZOLE NITRATE VAGINAL CREAM should work for you. If, however, you have never had these symptoms before, you should see your doctor before using MICONAZOLE NITRATE VAGINAL CREAM. **MICONAZOLE NITRATE VAGINAL CREAM IS FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS AND FOR THE RELIEF OF EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION. IT DOES NOT TREAT OTHER INFECTIONS OR EXTERNAL ITCHING AND IRRITATION DUE TO CAUSES OTHER THAN YEAST INFECTIONS. IT DOES NOT PREVENT PREGNANCY.**

WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?

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

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

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV—the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you may have been exposed to HIV and are experiencing either frequently recurring vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

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

SYMPTOMS OF VAGINAL YEAST INFECTIONS

There are many signs and symptoms of a vaginal yeast infection. They can include:

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

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

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast and in relieving vulvar itching and irritation associated with a yeast infection. Do not use in eyes or take by mouth.
- **DO NOT USE MICONAZOLE NITRATE VAGINAL CREAM IF YOU HAVE ANY OF THE FOLLOWING SIGNS AND SYMPTOMS. ALSO, IF THEY OCCUR WHILE USING MICONAZOLE NITRATE VAGINAL CREAM, 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 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.
- Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using MICONAZOLE NITRATE VAGINAL CREAM.
- 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

One tube of vaginal cream containing miconazole nitrate 2%. Seven disposable applicators.

Final Printed Labeling
ANDA 74-760
Educational Brochure
(Disposable Applicator-Back)

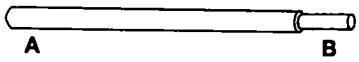
IMPORTANT: THE TUBE OPENING IS SEALED FOR YOUR PROTECTION. DO NOT USE IF THE TUBE SEAL HAS A HOLE IN IT OR IF THE SEAL CANNOT BE SEEN. RETURN THE PRODUCT TO THE STORE WHERE YOU BOUGHT IT.

DIRECTIONS FOR USE

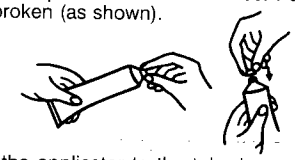
Vaginal Application

Begin treatment at bedtime. Before going to bed:

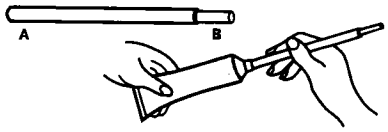
1 The first time you use a disposable applicator, pull the two pieces apart to see where the arrow is that indicates a full applicator. After locating the arrow, and before filling the applicator, push plunger "B" completely back inside "A". (Do not be concerned if the two come apart, they may easily be put back together.) See illustration.



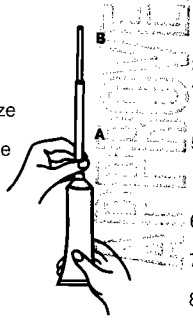
2 To open the tube, unscrew the cap. Turn the cap upside down and place the cap in the end of the tube. Push down firmly until the seal is broken (as shown).



3 Attach the applicator to the tube by pushing end "A" of the applicator over the neck of opened tube. Turn applicator, pushing down until applicator is firmly on the neck of the tube (as shown).



4 Hold applicator firmly on the tube neck. Squeeze the tube from the bottom. This will force the cream into the applicator. Do this until the inside portion of the applicator plunger "B" is pushed out to the tip of the "FULL" arrow or the beginning of the green band. Separate applicator from tube. (See illustration)



5 Hold the applicator containing the cream by the opposite end from where the cream 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 cream 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 cream. This will reduce leakage.

You may want to use deodorant-free minipads or pantyshields during the time that you are using MICONAZOLE NITRATE VAGINAL CREAM. This is because the cream can leak and/or you may see some discharge. DO NOT USE TAMPONS.

6 After each use, replace cap and roll tube from bottom (as shown).

7 Throw away the applicator after each use. DO NOT FLUSH IN TOILET. Use a new applicator for each dose.

8 Repeat steps 3 through 7 before going to bed on each of the next six evenings.

External Vulvar Application

If needed, use the cream twice daily as follows:

1. Squeeze a small amount of cream on to your finger.
2. Gently apply the cream onto the skin (vulva) that itches and is irritated.
3. Repeat steps 1 and 2 each morning and evening as needed.

ADVERSE REACTIONS (SIDE EFFECTS)

The following side effects have been reported with the use of MICONAZOLE NITRATE VAGINAL CREAM: a temporary increase in burning, itching, and/or irritation when the cream is inserted. Abdominal cramping, headaches, hives, and skin rash have also been reported. If any of these occur, stop using MICONAZOLE NITRATE VAGINAL CREAM and consult your doctor.

FOR BEST RESULTS

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

IF YOU HAVE A QUESTION

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

ACTIVE INGREDIENT

miconazole nitrate 2% (100 mg per dose)

STORAGE

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

Manufactured by:
Perrigo Co.
Allegan MI, 49010, U.S.A.

07/96
496053

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

MEDICAL REVIEW

DATE of ORIG. SUBMISSION:	SEPTEMBER 29,1995
OGD STAMP DATE:	OCTOBER 2, 1995
DATE RECEIVED BY HFD-520:	JANUARY 11, 1996
DATE of 1st AMENDMENT:	MARCH 20, 1996
DATE AMENDMENT RECEIVED:	APRIL 9, 1996
DATE of 2nd AMENDMENT:	OCTOBER 29, 1996
DATE of FIRST DRAFT:	OCTOBER 7 , 1996
DATE of SECOND DRAFT:	OCTOBER 30,1996
DATE COMPLETED:	DECEMBER 4, 1996

MEDICAL CONSULTATION FROM HFD-520

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Requested By: Office of Generic Drugs
HFD-600

APPEARS THIS WAY
ON ORIGINAL

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

Drug: Miconazole Nitrate Vaginal Cream 2%

Drug Category: Antifungal

Dose Form: Cream

Route of Administration: Vaginal

Dosage: One applicatorful (100 mg/dose) nightly for 7 consecutive nights

Materials Reviewed: 9/29/95 Submission
3/20/96 Amendment
10/29/96 Amendment
(also 10/1/96 and 10/4/96 amendments)

PURPOSE:

The purpose of this ANDA is to obtain approval for a generic form of Miconazole vaginal cream, manufactured by L. Perrigo Co., for the treatment of vaginal candidiasis. L Perrigo Co. is requesting that this approval be given based on a bioequivalency study comparing the safety and efficacy of their product with that of Monistat-7® 2% vaginal cream, manufactured by Ortho Pharmaceuticals.

Background:

Vaginal Candidiasis is among the most commonly diagnosed gynecological infections . The products currently available for the topical treatment of this infection belong either to the imidazole class of drugs, such as clotrimazole, miconazole and others, or to the polyenes, such as nystatin. These agents are available in the form of creams or suppositories for vaginal insertion.

Miconazole is a synthetic imidazole derivative that is fungicidal in vitro against species of the genus *Candida*. In 1973 it was approved for use in the treatment of vulvovaginal candidiasis as a prescription vaginal cream for daily use in a 7- day regimen (Monistat -7® Vaginal Cream). This agent has been available since 1990 as an over -the -counter product after the Fertility and Maternal Advisory Committee of the FDA concluded that recurrent vulvovaginal candidiasis could be self-recognized and safely and adequately treated by the female consumer.

The Applicant desires to make available to the consumer Miconazole 2% vaginal cream which they believe to be comparable in safety and efficacy to the presently- marketed Monistat-7® 2%(Ortho) vaginal cream.

Clinical Study:

In order to obtain approval for their product, the Applicant performed one comparative clinical trial entitled "A RANDOMIZED DOUBLE BLIND COMPARISON OF THE CLINICAL EFFICACY OF PERRIGO AND ORTHO (MONISTAT-7®) MICONAZOLE NITRATE 2% VAGINAL CREAM IN PATIENTS WITH VULVOVAGINAL CANDIDIASIS" designed to establish bioequivalence between a generic miconazole 2% vaginal cream, one applicatorful/100 mg/nightly for seven consecutive nights , and the approved preparation, Monistat-7 ®2% vaginal cream, administered nightly for 7 consecutive nights.

Study Design:

The study was a randomized, double-blinded, multicenter clinical trial designed to compare the clinical, mycological and therapeutic efficacy of the two(2) aforementioned miconazole vaginal creams in two(2) parallel groups of patients with vulvovaginal candidiasis. Patients with documented candidiasis were randomly assigned to one of the two(2) treatment groups.

Monitoring:

The study was conducted in accordance with the U.S. FDA " Draft Guidance for the performance of Bioequivalence Study for Vaginal Antifungal Products" (February 24,1990). The protocol was reviewed by the Bioequivalence Division of the FDA and the statistical portions of the protocol were developed in consultation with the Divisions of Bioequivalence and Biometrics of FDA. The study was monitored by [redacted] who contacted the Investigators prior to the initiation of the study in order to review the procedures to be followed in conducting the study and in the recording of results. The trials were monitored "as frequently as necessary" to ascertain adherence to the protocol. At the conclusion of the study, [redacted] was to return any unused supplies to the Sponsor.

Overview:

Potential Patients were to have had a screening assessment within 21 days prior to the initiation of the study in order to ascertain eligibility. This initial or Baseline Visit was to include a medical history, a brief physical exam, a gynecological exam including the obtainment of vaginal cultures for *Candida* species, *Neisseria gonorrhea*, *Chlamydia trachomatis* and *Gardnerella vaginalis*. A KOH prep was also obtained as well as a wet mount for *Trichomonas vaginalis*. Additionally, a urine b-HCG was performed.

If the patients were deemed eligible, a written informed consent was obtained. Patients were then randomized according to a predetermined block-type randomization scheme to receive one of the two formulations. Nine centers participated in the study and each center was randomized separately.

The patients received a supply of vaginal cream to be administered nightly for seven consecutive nights. The first day of therapy was **Day One** of the study. On **Day One** the patients were given a diary in which to record their medication usage including the time at which the medication was applied. Additionally they were to record any adverse events and the start and end of menses.

In order to establish clinical efficacy, evaluations of the affected areas were made at the preliminary visit (i.e. anytime within 21 days prior to **Day One**), to establish a baseline. The parameters evaluated included the presence or absence of the following signs (discharge, vulvar erythema, vaginal erythema, vulvar edema, vaginal edema, vulvar excoriation) and symptoms (discharge, itching, burning, irritation, dysuria, dyspareunia). The severity of each parameter was scaled on a 0-3 scale with 0=absent to 3=severe. A total symptom score and a total sign score were calculated with a range of 0 to18 respectively.

The first post-treatment visit (V1) was scheduled 7 days after the last treatment day, (range: 7-10 days) or for days 14-17 of the study. At this visit, the diaries were collected and reviewed, remaining supplies were collected and the patients were questioned about their symptoms, adverse drug reactions and unprotected sexual activity. The presence of clinical signs of vaginitis were assessed by the Investigator and a specimen was obtained for a KOH smear and fungal culture. Clinical and mycologic responses were recorded for each patient. Patients found to have a positive KOH smear or culture at V1 were recorded as failures and were not required to return for a second post-treatment visit.

The second post-treatment visit(V2) was scheduled for 28 days, (range: 28-34 days), after the last treatment day or days 35-41 of the study. At that time a gynecologic exam was performed, specimens were obtained for a KOH smear and fungal culture and the clinical signs of vaginitis were assessed. Patients were again requested to assess their symptoms and were questioned about sexual activity.

Medical Officer's Comment: The Medical Officer found that the way in which the applicant's handling of the post-treatment visits was not consistent with their stated intent. Although visits were planned within ranges accepted by this Agency, the patients were evaluated both early and late for both visits, well beyond the acceptable ranges, thus making them ineligible for evaluation. This practice diminished the number of evaluable patients as will be demonstrated in the Reviewer's assessment.

On October 1, 1996, the Medical Officer spoke with the Perrigo Company representative, Ginger Green and requested verification of the return visit dates. This information was provided, initially by phone and then by fax on Oct.29, 1996, and it was noted that the return visit dates represented the number of Days after completion of therapy, thus rendering unevaluable, 22 patients from the Ortho Monistat arm and 27 patients on the Perrigo arm.

Inclusion Criteria:

To be included in the study, patients had to fulfill all of the following criteria:

- Female patients between 18 and 50 years of age.
- Sexually active patients must fulfill one of the following:
  a. take oral contraceptives
  b. use other reliable forms of contraception (barrier and spermicide, IUD
  c. post-hysterectomy
  d. one year post-tubal ligation
  e. have only one sexual partner who must be at least one year post vasectomy;
- must be healthy aside from vaginal candidiasis.
- must agree to abstain from using vulvovaginal products (including lubricants) or medications during the course of treatment and until after the final cure assessment exam.
- must agree that all vagino-penile contact must be protected with a condom during the course of treatment and until after the final cure assessment exam.
- must have a negative beta-HCG urine pregnancy test prior to enrollment.
- Patients who expect their menses at any time during treatment or prior to V1 must agree to wait until menses are over to start treatment.
- must be able to complete all visits.
- must have an informed consent.
- must have at least one of the symptoms of vaginitis, as assessed by the patient (discharge, itching, burning, irritation, dysuria. dyspareunia).
- must have at least one of the clinical signs of vaginitis, as assessed by the investigator (discharge, vular/vaginal erythema and or edema, vulvar excoriation).
- must have a positive KOH prep and culture for *Candida* species.
- no concomitant infection of the vagina or vulva.

Exclusion Criteria:

- The presence of any of the following, excluded the patient from the study:
- Known sensitivity to Miconazole Nitrate or similar drugs.
- Post or peri-menopause.
- History of drug or alcohol abuse in the past year.
- Significant chronic illness of the cardiovascular, hepatic, gastro-intestinal, or central nervous system.
- Pregnancy or breast-feeding.
- History of genital *Herpes Simplex* infection.
- Vulvovaginal infections other than candidiasis. In particular, patients with positive cultures for *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria Gonorrhea, Gardnerella vaginalis.*
- Use of any vulvovaginal product or medication within the 48 hours prior to the first dose or at any time during treatment.
- Use of any systemic or topical anti-infective, anti-mycotic, cortico-steroid or immuno-suppressive drugs in the previous week.
- Anatomic anomaly likely to impede the therapeutic effects.
- Personality disorders which would preclude valid informed consent or compliance.
- Persistent vaginal infections in the previous three months.

Medical Officer's Comment: The Medical Officer's found that ~~that~~ 5 patients included in the efficacy analysis by the Applicant were receiving concomitant antibiotic therapy, (Perrigo024,045, and Ortho139,151,245) and felt that they should be excluded based on a protocol violation..

Evaluability Criteria:

Patients were evaluable for the efficacy analysis if they had satisfied all if the eligibility criteria, received the study medication as per protocol and had returned for both post-treatment visits within the stated intervals. *The Medical Officer decided a priori to accept a range of 6-11 days post therapy for visit 1 (or days 13-18 of the study) and a range of 27-35 days post therapy for visit 2 (or days 34-42 of the study).*

The protocol did not provide for a minimum number of days required on therapy necessary for evaluability. *The Medical Officer included all patients who received a minimum of 3 days of therapy in the efficacy analysis.*

Patients were evaluable for safety if they received at least one dose of either study drug , even if they subsequently discontinued treatment.

Endpoints/Cure Assessments:

The protocol states the following as definitions of cure/efficacy:

Mycological Cure:

A negative KOH prep and culture for Candida species at **both** of the post-treatment visits.

Clinical Cure:

Significant improvement in the signs and symptoms that were present at the initial visit by V1 and resolution by V2. Additionally, the sponsor states that if no significant improvement or a worsening is observed at V1, the patient will be considered a treatment failure and discharged from the study.

Medical Officer's Comment: The review revealed that 6 patients, considered clinical failures by the applicant (Ortho 190,155, Perrigo 219,116,052,235) could have been clinical cures, given the presence of minimal signs and symptoms at V2. Because the information was not provided in the submission, the MO communicated by phone with Ginger Green on 10/4/96 and requested more information. This information was provided, initially by fax and then as an amendment. The MO was able to independently verify the evaluability of the above patients from the fax submission dated October 30, 1996. Based on the line listings provided, patients 116, 052, 219, 190, and 155 were considered cures.

Overall/Therapeutic Outcome:

A patient who is considered to have both clinical and mycological cure will be used to determine the overall cure rate.

The reviewing Medical Officer considers the clinical and mycological cure rates as secondary efficacy variables and that the primary efficacy variable to be the therapeutic cure rate.

Safety evaluation:

The patients and investigators were required to report all adverse events in a timely fashion . The investigator determined the intensity of the event and its relation to the study drug.

Study Results:

The study was conducted at 9 clinical sites in the province of Quebec, Canada. There were a total of 12 investigators, 8 of whom were Ob/Gyn's, three General Practitioners and one Internist with Ob/Gyn privileges. A total of 221 patients were enrolled, 197 completed the study and 165 were deemed evaluable for the efficacy analysis by the Investigator. Of these patients, 110 were randomized to receive the Perrigo vaginal cream and 111 to receive the Ortho Monistat-7 vaginal cream.

As stated above all 221 patients were included in the safety analysis and 165 were deemed eligible for the efficacy analysis. 56 patients were excluded from the efficacy analysis for a variety of protocol violations, including 12 with a negative KOH prep at the initial visit, 17 who had a missing KOH prep at any visit, 13 who had violations of the inclusion/exclusion criteria, 6 protocol violations while on study , 3 who were non-compliant, 1 pregnancy and 4 patients failed to return. Of the 165 patients included in the efficacy analysis, 83 were randomized to the Perrigo vaginal cream and 82 to the Ortho vaginal cream.

Below is the Applicant Analysis of Patient Evaluability, which includes the investigators, the numbers of enrolled patients and evaluable patients by Center.

TABLE 1

APPLICANT'S EVALUABILITY

	PERRIGO RECIPIENTS			ORTHO RECIPIENTS			ALL RECIPIENTS		
Center/Investigator	EVAL.	ENROLL.	% EVAL.	EVAL.	ENROLL.	% EVAL.	EVAL.	ENROLL.	% EVAL.
[redacted]	30	43	70%	30	43	70%	60	86	70%
	14	21	67%	16	19	84%	30	40	75%
	4	6	67%	3	6	50%	7	12	58%
	1	2	50%	2	3	67%	3	5	60%
	11	12	92%	7	11	64%	18	23	78%
	7	9	78%	5	9	56%	12	18	67%
	8	8	100%	7	8	88%	15	16	94%
	2	2	100%	4	4	100%	6	6	100%
	6	7	86%	8	8	100%	14	15	93%
TOTAL	83	110	75%	82	111	74%	165	221	75%

Reasons for Exclusion by Applicant:	Perrigo	Ortho
Negative KOH Prep/culture on admission:	6	6
Missing KOH Prep/culture at any visit:	10	7
Protocol violation (incl./excl.):	3	10
Lost to Follow-up:	2	2
On Study Protocol Violation:	5	1
Patient Non-compliance:	1	2
Patient found to be pregnant:	1	0
TOTAL:	28 *	28 *

There were large differences in the sample sizes collected from each Center , however the sponsor felt that the overall rates of cure/failure were similar and therefore the data from all centers was pooled for statistical analysis.

**The MO found it impossible to explain the difference of 1 patient between the 2 groups excluded by the Applicant. There should only be 27 patients excluded from the Perrigo arm and 29 from the Ortho, however it does not appear as if this difference is significant.*

The Medical Officer's Analysis of the patients is presented in Table 2:

TABLE 2
MO'S EVALUABILITY

Center/Investigator	PERRIGO RECIPIENTS			ORTHO RECIPIENTS			ALL RECIPIENTS		
	EVAL	ENROLL	% EVAL	EVAL	ENROLL	% EVAL	EVAL	ENROLL	% EVAL
	25	43	58%	27	43	63%	52	86	60%
	2	21	10%	7	19	37%	9	40	23%
	1	6	17%	1	6	17%	2	12	17%
	0	2	0%	1	3	33%	1	5	20%
	5	12	42%	4	11	36%	9	23	39%
	6	9	67%	2	9	22%	8	18	44%
	7	8	88%	6	8	75%	13	16	81%
	2	2	100%	2	4	50%	4	6	67%
	5	7	71%	7	8	88%	12	15	80%
TOTAL	53	110	48%	57	111	51%	110	221	50%

Of note is that of the 83 Perrigo patients included by the Applicant in the patients evaluable for efficacy, only 53 were acceptable by the MO.

Of the 83 Perrigo patients, 2 Patients (045, 245), were excluded because of concurrent systemic Antibiotic usage, 27 were excluded because of too early or too late follow-up visits and 1, (No. 152) , was excluded because she self-collected her culture at V2. Hence 30 Perrigo patients were deemed unevaluable.

Of the 82 Ortho patients included by the Applicant in the efficacy analysis, only 57 were deemed evaluable by the Medical Officer and 25 were deemed unevaluable: 3, (024,151,139), were excluded for concurrent systemic Antibiotic usage and 22 for untimeliness of the revisits.

Below, in tabular form ,(Table 3), is a listing of the patients who were excluded by the Medical Officer for protocol violations (the dates of the return visits are noted where they were out of range as well as the concomitant antibiotic usage. In some cases the patients could have been excluded for more than 1 violation):

TABLE 3

MEDICAL OFFICER'S TABLE OF NONEVALUABILITY

Ortho Arm: (n=25)

Patient Number	V1 (Days 13-18 accepted)	V2 (Days 34-36 accepted)	Concomitant Antibiotic Usage
021	20	48	NO
024			YES
046	20	37	NO
050	30	37	NO
056	19	41	NO
061	23	50	NO
064	11	39	NO
073	11	37	NO
109	9	39	NO
115	19	No V2	NO
118	11	30	NO
121	19		NO
139		38	YES
151			YES
160	19	48	NO
166		49	NO
170	20	41	NO
174	11	31	NO
182	21	49	NO
187	24	52	NO
188		64	NO
081	11	26	NO
242		31	NO
236	21	43	NO
237	21	43	NO

TABLE 3

Perrigo Arm: (n-30)

Patient Number	V1 (Days 13-18 accepted)	V2 (Days 34-36 accepted)	Concomitant Antibiotic Usage
016	11		NO
020		29	NO
022	12	54	NO
023	21	87	NO
029		46	NO
045	21	39	YES
051	20	37	NO
053		30	NO
055	22		NO
057		53	NO
062	10	43	NO
080	12	39	NO
107	21	37	NO
113		46	NO
120	11		NO
123	19		NO
124		33	NO
126		44	NO
142		31	NO
152		40	NO, but self-collected specimen
157	18	47	NO
167		45	NO
168		44	NO
173	11	37	NO
178		47	NO
185		44	NO
186	12	39	NO
197		51	NO
241	11	39	NO
245		37	YES

Demographics:

The demographics of the enrollees have been provided and reveal no significant differences between Centers. It is this Reviewer's opinion that it is acceptable to pool the data as there do not appear to be significant differences between the populations enrolled. It was noted that there were differences in the quality of reporting between centers. This variability was not considered significant.

Below is the Applicant's Table of Demographic Data for evaluable patients:

TABLE 4

	Perrigo	Ortho
Mean Weight (kg)	63.0	62.7
	n=(82)*	(n=82)
(range)	(40.8-120.3)	(45.4-113.9)
Mean Height (cm)	160.1	161.2
	(n=74)*	(n=73)*
(range)	(110.0-178.0)	(125.0-177.0)
Mean age (years)	32.0	31.8
	(n=83)	(n=82)
(range)	(18.0-49.0)	18.0-50.0)

*The height was not determined for 9 patients on both arms of the study and the weight was not determined for 1 patient who received the Perrigo drug.

Efficacy Analysis:

The results as submitted by the Applicant are shown below:

TABLE 5
APPLICANT"S EFFICACY ANALYSIS

Treatment Group	Perrigo	Ortho
Mycological Cure	70/82 (85.4%)	66/82 (80.5%)
KOH/culture V1	73/83 (88.0%)	75/82 (91.5%)
KOH/culture V2	71/75 (94.7%)	66/78 (84.6%)
Clinical cure		
V1	81/83 (97.6%)	78/82 (95.1%)
V2	68/75 (90.7%)	75/78 (96.2%)
Therapeutic Cure	58/83 (69.9%)	57/82 (69.5%)

It should be noted that mycological cure was defined as negative KOH Preps and cultures for *Candida* species at both V1 and V2. Clinical cure rates were based on assessments indicating improvement at V1 and complete eradication of all signs and symptoms at V2. Therapeutic Cure could only be determined at the last visit (V2) . Patients who were considered treatment failures at V1 did not return for V2 and therefore the number of patients evaluated at V2 is smaller than the number evaluated at V1 in both treatment groups. *Additionally the culture information was lost for 1 Perrigo patient (086) at V1 and thus the number of patients evaluated for the Perrigo arm of the study, decreased by 1.* The above is a reproduction of the Applicant's table. Although the Applicant provided the above italicized explanation for the change in the Perrigo denominator for 83 to 82, it is not clear to the MO, why the denominator was changed. However, this change does not appear to alter the results or to be of significance.

Medical Officer Results:

Mycological cure was assessed at V1 and V2. Clinical cure, as evidenced by improvement in the signs and symptoms score was assessed at V1 and as evidenced by a 0-3 sign and symptom score was assessed at V2. Six patients, (4 on the Perrigo arm and 2 on the Ortho arm) were assessed in more detail because of the possibility of a change in their final status re their sign/symptom scores. *Three of the Perrigo patients and two of the Ortho patients were reassessed as clinical cures by the Medical Officer because of the presence of a low score on the final clinical assessment.* This score represented the presence of a discharge only, without other findings and in the presence of negative cultures.

Therapeutic cure could only be assessed at V2. This assessment is presented in tabular form below.

Patients who were considered mycological treatment failures at V1 were withdrawn from the study. No data were obtained by the sponsor for these patients at V2 and therefore they were excluded from the therapeutic efficacy analysis by the Applicant. *The Medical Officer determined that these patients should be included in the Therapeutic Analysis, as failures.*

TABLE 6

MEDICAL OFFICER"S EFFICACY ANALYSIS

Treatment Group	Perrigo			Ortho		
	Cure	No. eval		Cure	No. eval.	
Mycological Cure	41	53	77.4%	47	57	82.5%
KOH/Culture V1	43	52	82.7%	52	57	91.2%
KOH/Culture V2	42	53	79.2%	48	57	84.2%
Clinical Cure V1	52	53	98.1%	52	57	91.2%
Clinical Cure V2	40	53	75.5%	48	57	84.2%
Therapeutic cure	40	53	75.5%	43	57	75.4%

Safety Evaluation:

71 adverse events were recorded for patients who received the Perrigo product and 74 for those who received the Ortho product. Of these , 2 were considered serious by the Investigator and were judged not to be related to the study medication. The Medical Officer concurs with the Investigator's opinion after reviewing the case report forms for these 2 events.

Presented below, in tabular form, (Table 7), is a summary of the adverse events reported and their causal relationship to the study medication.

TABLE 7

ADVERSE EVENTS (according to Applicant)

Symptoms	Perrigo	Ortho	Relationship
Rash		1	unrelated
Nausea		1	unrelated
vulvar ulcer		1	unrelated
swelling		1	unrelated
dark stool		1	unrelated
staining	1		unrelated
abdominal pain	8	6	unrelated
cervical Chlamydia	1		unrelated
gastritis	1		unrelated
cold sensation	3		remote
burning	30	24	possible
itching	14	19	possible
discharge	1	1	unrelated
vaginal bleeding	1		unrelated
urinary frequency/UTI	3	3	unrelated
headache	1	6	unrelated
URI symptoms	7	10	unrelated
Total	71	74	

As noted in Table 7, there were 71 adverse events in 40 patients on the Perrigo arm and 74 in 41 patients on the Ortho arm.

90% Confidence Interval

TABLE 8

ANDA NUMBER: 74-760
TREATMENT INDICATION: vaginal candidiasis

TIME OF ASSESSMENT: VISIT 2
CLINICAL/MICRO?: therapeutic

	Success Rate	Number of Evaluable Pts.	Number of Successes
Test drug	0.755	53	40
Comparator	0.754	57	43
Difference	-0.000	Diff. in % =	**-0.03**
SE(d)	0.082		

W/ CONTINUITY CORRECTION FACTOR: **90% CI= { -15.30 , 15.36 }**
(In Percentages)
WITHOUT CORRECTION FACTOR: **90% CI= { -13.48 , 13.54 }**

The 90% confidence interval for the primary efficacy variable of therapeutic cure rate is within the required interval of ±0.20 as illustrated above.

Summary:

This was a randomized double-blinded, multi-center clinical trial undertaken to compare the safety and efficacy of a generic form of Miconazole cream, manufactured by L. Perrigo Co., for the treatment of vulvovaginal Candidiasis. The comparator treatment regimen was Monistat-7®, miconazole vaginal cream, manufactured by Ortho Pharmaceuticals.

221 patients were enrolled and randomly assigned to a treatment arm. Of these, 165 were deemed eligible for the efficacy analysis by the Applicant. 83 patients received the Perrigo drug and 82 received Monistat-7®. The reviewing Medical Officer excluded 2 patients from the Perrigo arm because of concurrent antibiotic usage , one patient because she self-collected her final specimen and 27 because of failure to present for follow-up within the extended intervals permitted in the evaluation of vaginal Antifungal products. Additionally, from the Ortho arm, 3 patients were excluded because of concurrent antibiotic usage, and 22 for failure to present within the aforementioned time intervals. Therefore the Medical Officer considered 53 Perrigo patients and 57 Ortho patients evaluable for efficacy.

In the Applicants' analysis, patients who were considered treatment failures at V1 were not included in the number of evaluable patients at V2. The Medical Officer determined that these patients were evaluable at V2 and carried forward as treatment failures. Additionally, the MO, disagreed with the Applicant's scoring of 3 Perrigo patients and 2 Ortho patients as clinical failures. A review of the signs and symptoms revealed that these patients were clinical cures. Otherwise, the MO agreed with the Applicant's scoring of cures and treatment failures, as provided in the 3/20/96 and the 10/29/96 amendments.

Mycological Cure Rates reported by the Applicant for V2 were 85.4% for the Perrigo product and 80.5% for the Ortho. The Medical Officer found a 77% cure rate for the Perrigo group and an 84% cure rate for the Ortho group.

Clinical cure rates reported by the Applicant for V2 were 90.7% for the Perrigo product and 96.2% for the Ortho product. The MO found a 75% cure rate for the Perrigo product and an 84% for the Ortho product at V2.

Therapeutic/overall cure rates reported by the Applicant were 69.9% for the Perrigo treatment group and 69.5% for the Ortho treatment group. The MO found that the therapeutic cure rates were 75% for the Perrigo group and 75% for the Ortho group. Using the 90% CI approach, the limits (using correction for continuity) around the difference between the 2 treatment arms are (-15.30, 15.36).

The data submitted by the Applicant have been verified and reanalyzed by the reviewing Medical Officer and a statistical consultation has been requested. The criterion for establishing bioequivalency for generic drugs is that the upper and lower limits of the 90% confidence interval of the difference between the 2 products be within the interval of ±0.20. In this submission the 90% confidence interval for the primary efficacy variable (therapeutic cure) has been met.

Conclusion:

The formulations of Miconazole vaginal cream manufactured by the L.Perrigo and Co. and Ortho Pharmaceuticals Corp. are equivalent in safety and efficacy for the treatment of recurrent vulvovaginal candidiasis for 7 days.

Recommendation:

The reviewing Medical Officer recommends approval of ANDA 74-760

/S/

Regina Alivisatos, MD
Medical Officer

CC: ANDA 74-760
HFD-630
HFD-340
HFD-520
HFD-520/MO/Ralivisatos
HFD-520/Biostats/DLin
HFD-520/CSO/STrostle

Concurrence Only:
HFD-520/Dir./DFeigal
HFD-520/SMO/BLeissa

/S/ 1.28.97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 74-760

3. NAME AND ADDRESS OF APPLICANT

L. Perrigo Company
117 Water Street
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION

The firm has indicated that in their opinion and to the best of their knowledge there are no patents that claim the listed drug product referred to in this application or that claim a use of the listed drug product and there is no market exclusivity information on file for the listed drug product MONISTAT 7 Combination pack.

NOTE:

The combination pack is not the RLD. Firm will be told to correct.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Miconazole Nitrate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Original 9/29/95
Amendment 11/1/95
Amendment 12/22/95
Amendment 1/31/96

10. PHARMACOLOGICAL CATEGORY

treatment of vaginal yeast infections

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

DMF's [redacted]

13. DOSAGE FORM

Cream

14. POTENCY

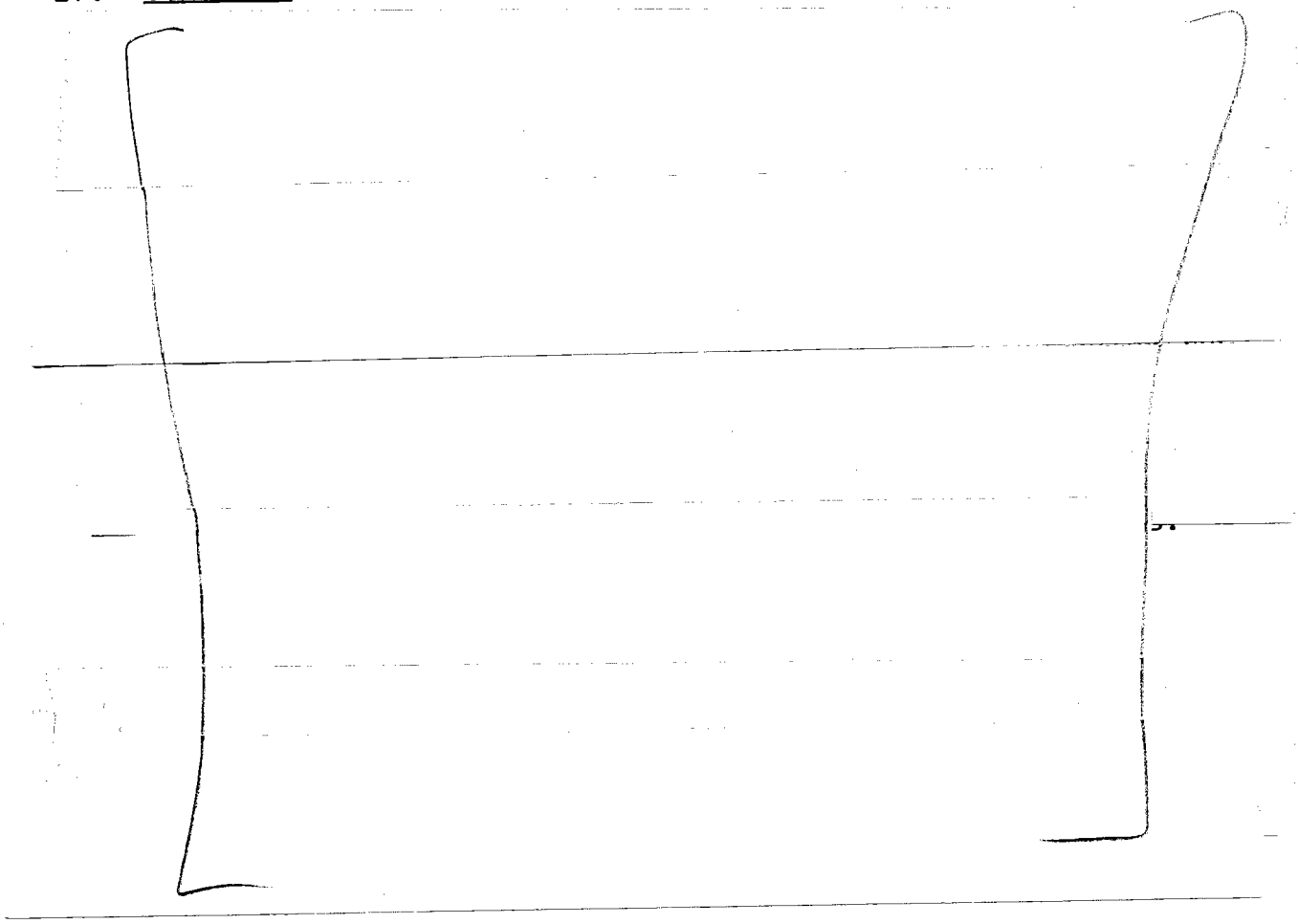
2%

15. CHEMICAL NAME AND STRUCTURE

1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxyl]ethyl]-, mononitrate

16. RECORDS AND REPORTS

17. COMMENTS



18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER:	DATE COMPLETED:
Nashed E. Nashed, Ph.D.	3/15/96
Supervisor: Paul Schwartz, Ph.D.	5/15/96

Redacted 8

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-760

3. NAME AND ADDRESS OF APPLICANT

L. Perrigo Company
117 Water Street
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION

In the firm opinion and to the best of their knowledge there are no patents that claim the listed drug product referred to in this application or that claim a use of the listed drug product.

The firm has revised the exclusivity statement to indicate that there is no market exclusivity for Monistat 7 vaginal cream.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Miconazole Nitrate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Original 9/29/95
Amendment 11/1/95
Amendment 12/22/95
Amendment 1/31/96
Amendment 3/20/96
Amendment 8/9/96
Amendment 10/16/96
Amendment 10/29/96
Amendment 4/15/97

APPEARS THIS WAY
ON ORIGINAL

10. PHARMACOLOGICAL CATEGORY

treatment of vaginal yeast infections

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

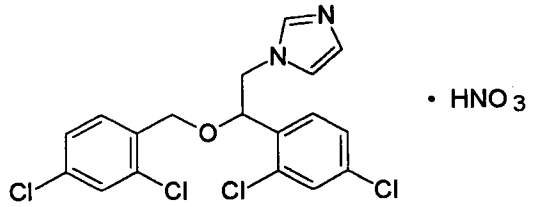
Cream

14. POTENCY

2%

15. CHEMICAL NAME AND STRUCTURE

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



17. COMMENTS

APPEARS THIS WAY
ON ORIGINAL

18. CONCLUSIONS AND RECOMMENDATIONS

The Application is APPROVABLE.

19. REVIEWER:

/S/

Nashed E. Nashed, Ph.D.

DATE COMPLETED:

4/21/97

4/16/97

Supervisor: Paul Schwartz, Ph.D.

X:\NEW\FIRMSNZ\PERRIGO\LTRS&REV\74760.3

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pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

STATISTICAL REVIEW(S)

Attachment-2

Statistical Review and Evaluation
(Consult)

ANDA#: 74-760 DEC 9 1996

Applicant: L. Perrigo Co.

Name of Drug: Miconazole Nitrate Vaginal Cream 2%

Documents Reviewed: Medical Officer's Review, received Dec. 4, 1996

Indication: Vaginal Candidiasis

Medical Input: Dr. Regina Alivisatos, HFD-520

A. INTRODUCTION

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

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

B. CALCULATIONS AND EVALUATION

All calculations are based on the RMO's data as supplied on December 4, 1996. All confidence interval results are presented as two-sided 90% confidence intervals in the format $_{n_t, n_c}(CI)_{p_t, p_c}$, where n_t and p_t are respectively the sample size and success rates for the test agent (Perrigo's product - miconazole nitrate vaginal cream 2%) and n_c and p_c are similarly defined for the control agent (Ortho's product - Monistat-7® 2% vaginal cream).

The therapeutic response rate is the primary efficacy criterion and the ~~my~~cological and clinical response rates are the secondary efficacy criteria.

The following CIs are based on the Medical officer's data. For clinical response at the first post-treatment visit (V1), the Perrigo versus Ortho 90% CI is $_{53,57}$ (-.018, .156)$_{.98,.91}$. At second post-treatment visit (V2) the Perrigo versus Ortho 90% CI is $_{53,57}$ (-.23, .056)$_{.75,.84}$. For mycological response at the second post-treatment visit (V2), the Perrigo versus Ortho 90% CI is $_{53,57}$ (-.195, .093)$_{.77,.82}$.

For therapeutic response at second post-treatment visit (V2), the Perrigo versus Ortho 90% CI is $_{53,57}$ (-.153 .154)$_{.75,.75}$.

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

Except the clinical cure rates at second post-treatment (V2), all of the 90% CIs for the secondary efficacy variables of mycological and clinical cure rates do meet the Generic Drug equivalency criteria of $\pm$ 0.20. For the primary efficacy response, the 90% CIs for the therapeutical cure rates also meet the Generic Drug equivalency criteria of $\pm$ 0.20.

The results of the analyses of data derived from the RMO's review support the sponsor's claim that their formulation of Miconazole nitrate vaginal cream 2% is therapeutically equivalent to that of Monistat-7® 2% (Ortho) vaginal cream.

/S/ 12/9/96

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

cc:
Orig. ANDA 74-760
HFD-520
HFD-520/Dr. Feigal
HFD-520/Dr. Leissa
HFD-520/Dr. Alivisatos
HFD-520/Mr. Trostle
HFD-630/Ms. Parise
HFD-725/Dr. Harkins
HFD-725/Dr. Lin
Chron.
This review contains two pages.
WordPerfect 6.1/A74760.wp6/12-9-96

Attachment - 3

THE PERRIGO COMPANY
ANALYTICAL SERVICES
SPECIAL ASSAY REPORT

No. 10221

SAMPLE (S): MICONAZOLE NITRATE VAGINAL CREAM 2%

PRODUCT CODE: 214AA **LOT:** 4BH172

SOURCE: [redacted] **REQUESTED BY:** [redacted]

TESTED BY: [redacted] **REFERENCE:** AD159p2,3

COMMENTS

Analytical was requested by [redacted] to compare the physical characteristics of Perrigo's Miconazole Nitrate Vaginal Cream 2% to marketed products from two other manufacturers. The samples included Perrigo's test batch(PC#214AA, Lot#4BH172) and the reference batch(Monistat 7, Lot#24B904B) used in the bio-equivalency study.

TESTS	PERRIGO Lot#4BH172	COPLEY Lot#4SF873	Monistat 7 Lot#24B904B
WATER	[redacted]	[redacted]	[redacted]
SOLIDS	[redacted]	[redacted]	[redacted]
VISCOSITY	[redacted]	[redacted]	[redacted]
pH	[redacted]	[redacted]	[redacted]
SPECIFIC GRAVITY	[redacted]	[redacted]	[redacted]

PREPARED BY: /S/ **DATE:** 11/7/95 **CKD BY:** /S/

COPIES: [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-760 SPONSOR: L. Perrigo Co..

DRUG AND DOSAGE FORM: Miconazole Nitrate Vaginal Cream
STRENGTHS(s): 2% Cream
TYPE OF STUDY: Comparative Clinical Study
STUDY SITE:

STUDY SUMMARY: Bioequivalence between the test and reference (Ortho's , 2% Vaginal creams) products was determined on the basis of comparative clinical study. The medical and statistical evaluations indicate, that except for clinical cure rate on the third visit, mycologic, clinical and therapeutic cure rates for Perrigo and Ortho miconazole nitrate vaginal creams are equivalent, and the products meet the criteria of 90% confidence interval of 80-120%. No serious adverse reactions were observed.

L. Perrigo and Ortho's , 2% vaginal cream formulations are qualitatively identical, but varied quantitatively. All inactive ingredients are within the IIG 1996 limits

Physicochemical properties for test, Copley (generic), and reference products were similar

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

DISSOLUTION: Not required.

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

INITIAL /S/ DATE 3/5/97

BRANCH CHIEF: Shriniwas. G. Nerurkar, Ph.D. BRANCH: II
INITIAL: /S/ DATE 3/6/1997

for DIRECTOR
DIVISION OF BIOEQUIVALENCE: Nicholas M. Fleischer, Ph.D.
INITIAL: /S/ TE 3/6/97

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL /S/ DATE 3/11/97

Table 1. Comparative Formulation

Ingredients	L. Perrigo mg/g	Ortho USA mg/g
Miconazole nitrate, USP	20.0	20.0
Benzoic Acid USP	[redacted]	PNG[1]
BHA	[redacted]	PNG[1]
Glyceryl Monostearate	[redacted]	PNG[1]
Mineral Oil, NF	[redacted]	PNG[1]
Peglicol 5 Oleate	[redacted]	PNG[1]
Pegoxol 7 Stearate	[redacted]	PNG[1]
Purified Water, USP	[redacted]	

1 Potency not given.

MAR 6 1997

ANDA # 74-760
Miconazole Nitrate Vaginal Cream, 2%
Reviewer: S. P. Shrivastava
WP # 74760S.995

L. Perrigo Co.
Allegan, MI
Submission Date:
September 29, 1995
3/20/96; 10/1/96
10/4/96; 10/29/96

REVIEW OF A BIOEQUIVALENCE STUDY

The firm has resubmitted the comparative clinical study for its OTC miconazole nitrate vaginal cream, 2%, which was reviewed by the Division of Anti-Infective Drug Products (HFD-520) and Biometrics IV (HFD-725). The consults' reviews are attached (Attachments 1-2). Comparative composition of the formulations are given in Table 1.

COMMENTS

1. 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 except for clinical cure rate on the third visit, mycologic, clinical and therapeutic cure rates for Perrigo and Ortho miconazole nitrate vaginal creams are equivalent. The parameter values were obtained at second (V2) and third (V3) visits, and were statistically analyzed using 90% CI criteria.

2. The inactive ingredients in L. Perrigo's 2% miconazole nitrate vaginal cream, and Ortho's Monistat-7^R 2% vaginal cream, are qualitatively identical and quantitatively different. All inactive ingredients are within the IIG 1996 limits [redacted]

3. The physicochemical properties including viscosity, pH and specific gravity of L. Perrigo, Copley (generic), and Ortho (innovator) products are quite similar.

4. The lot size was [redacted]

RECOMMENDATION

The comparative clinical study conducted by L. Perrigo Co., on its miconazole nitrate vaginal cream, 2%, Lot # 4BH172, comparing it to Ortho's Monistat-7 Cream, 2%, Lot # 24C909 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 cream, 2%, is bioequivalent to the reference product, Monistat-7^R vaginal cream, 2%, 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 SNerurkar
FT INITIALED SNerurkar

/S/ Date 3/6/1997

Concur: /S/ Date: 3/6/97

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

Attachment-3

SPS/sps/2-12-97/74760S.995

cc: ANDA #74-760 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Div. File

APPEARS THIS WAY
ON ORIGINAL

Table 1. Comparative Formulation

Ingredients	L. Perrigo mg/g	Ortho USA mg/g
Miconazole nitrate, USP	20.0	20.0
Benzoic Acid USP	[redacted]	PNG[1]
BHA	[redacted]	PNG[1]
Glyceryl Monostearate	[redacted]	PNG[1]
Mineral Oil, NF	[redacted]	PNG[1]
Peglicol 5 Oleate	[redacted]	PNG[1]
Pegoxol 7 Stearate	[redacted]	PNG[1]
Purified Water, USP	[redacted]	q.s.

APPEARS THIS WAY
ON ORIGINAL

1 Potency not given.

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

Project Number 901368
Subject classification list

Subject	Class	Code
1	COMPLETED PATIENT	1
2	TREATMENT FAILURE	4b
3	COMPLETED PATIENT	1
4	COMPLETED PATIENT	1
5	COMPLETED PATIENT	1
6	COMPLETED PATIENT	1
7	COMPLETED PATIENT	1
8	COMPLETED PATIENT	1
9	ADVERSE REACTION	5
10	COMPLETED PATIENT	1
11	TREATMENT FAILURE	4a
12	COMPLETED PATIENT	1
13	COMPLETED PATIENT	1
14	COMPLETED PATIENT	1
15	TREATMENT FAILURE	4a
16	COMPLETED PATIENT	1
17	COMPLETED PATIENT	1
18	COMPLETED PATIENT	1
19	COMPLETED PATIENT	1
20	TREATMENT FAILURE	4a
21	NOT ELIGIBLE FOR STUDY	3c
22	TREATMENT FAILURE	4a
23	COMPLETED PATIENT	1
24	TREATMENT FAILURE	4a
25	COMPLETED PATIENT	1
26	NOT ELIGIBLE FOR STUDY	3c
27	LOST TO FOLLOW-UP OR MISSING DATA	2a
29	COMPLETED PATIENT	1
30	COMPLETED PATIENT	1
31	LOST TO FOLLOW-UP OR MISSING DATA	2a
32	COMPLETED PATIENT	1
33	COMPLETED PATIENT	1
34	COMPLETED PATIENT	1
35	LOST TO FOLLOW-UP OR MISSING DATA	2b
36	TREATMENT FAILURE	4b
37	TREATMENT FAILURE	4b
38	COMPLETED PATIENT	1
39	TREATMENT FAILURE	4b
40	TREATMENT FAILURE	4b
41	COMPLETED PATIENT	1
42	COMPLETED PATIENT	1
43	COMPLETED PATIENT	1
44	COMPLETED PATIENT	1

1-Patient completed all 3 visits and has data from 3 KOH+3 culture results
2a- Patient came for Visit 1 only. 2b- Patient came for Visits 1+2 only
2c- Missing KOH/culture at any visit. 2d- Came too late for Visit 2 or 3
3a- Protocol violation (inc/exc) 3b- Asymptomatic at Visit 1
3c- Negative KOH/culture at Visit 1 4a- Positive KOH/culture at Visit 2
4b- Positive KOH/culture at Visit 3 5-Patient withdrew from study due to ADR

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

Project Number 901368
Subject classification list

Subject	Class	Code
45	COMPLETED PATIENT	1
46	COMPLETED PATIENT	1
47	COMPLETED PATIENT	1
48	COMPLETED PATIENT	1
49	NOT ELIGIBLE FOR STUDY	3a
50	COMPLETED PATIENT	1
51	COMPLETED PATIENT	1
52	TREATMENT FAILURE	4a
53	COMPLETED PATIENT	1
54	LOST TO FOLLOW-UP OR MISSING DATA	2b
55	LOST TO FOLLOW-UP OR MISSING DATA	2a
59	COMPLETED PATIENT	1
60	COMPLETED PATIENT	1
61	COMPLETED PATIENT	1
62	TREATMENT FAILURE	4b
63	COMPLETED PATIENT	1
64	COMPLETED PATIENT	1
65	TREATMENT FAILURE	4b
66	TREATMENT FAILURE	4b
67	LOST TO FOLLOW-UP OR MISSING DATA	2a
68	LOST TO FOLLOW-UP OR MISSING DATA	2b
69	TREATMENT FAILURE	4a
70	LOST TO FOLLOW-UP OR MISSING DATA	2b
71	NOT ELIGIBLE FOR STUDY	3c
72	TREATMENT FAILURE	4b
73	NOT ELIGIBLE FOR STUDY	3c
74	COMPLETED PATIENT	1
75	COMPLETED PATIENT	1
76	COMPLETED PATIENT	1
77	LOST TO FOLLOW-UP OR MISSING DATA	2d
78	NOT ELIGIBLE FOR STUDY	3c
79	TREATMENT FAILURE	4b
80	COMPLETED PATIENT	1
81	TREATMENT FAILURE	4b
82	COMPLETED PATIENT	1
83	COMPLETED PATIENT	1
84	TREATMENT FAILURE	4b
85	COMPLETED PATIENT	1
86	NOT ELIGIBLE FOR STUDY	3c
87	COMPLETED PATIENT	1
88	COMPLETED PATIENT	1
89	COMPLETED PATIENT	1
90	LOST TO FOLLOW-UP OR MISSING DATA	2d

1-Patient completed all 3 visits and has data from 3 KOH+3 culture results
2a- Patient came for Visit 1 only. 2b- Patient came for Visits 1+2 only
2c- Missing KOH/culture at any visit. 2d- Came too late for Visit 2 or 3
3a- Protocol violation (inc/exc) 3b- Asymptomatic at Visit 1
3c- Negative KOH/culture at Visit 1 4a- Positive KOH/culture at Visit 2
4b- Positive KOH/culture at Visit 3 5-Patient withdrew from study due to ADR

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
Subject classification list

Subject	Class	Code
91	COMPLETED PATIENT	1
92	COMPLETED PATIENT	1
93	COMPLETED PATIENT	1
94	COMPLETED PATIENT	1
95	TREATMENT FAILURE	4b
96	COMPLETED PATIENT	1
97	TREATMENT FAILURE	4a
98	COMPLETED PATIENT	1
99	COMPLETED PATIENT	1
100	COMPLETED PATIENT	1
102	COMPLETED PATIENT	1
104	COMPLETED PATIENT	1
105	TREATMENT FAILURE	4b
107	NOT ELIGIBLE FOR STUDY	3c
109	NOT ELIGIBLE FOR STUDY	3c
110	COMPLETED PATIENT	1
111	COMPLETED PATIENT	1
112	COMPLETED PATIENT	1
119	COMPLETED PATIENT	1
121	COMPLETED PATIENT	1
122	COMPLETED PATIENT	1
123	COMPLETED PATIENT	1
124	COMPLETED PATIENT	1
125	NOT ELIGIBLE FOR STUDY	3c
126	COMPLETED PATIENT	1
127	COMPLETED PATIENT	1
128	COMPLETED PATIENT	1
129	COMPLETED PATIENT	1
130	COMPLETED PATIENT	1
131	NOT ELIGIBLE FOR STUDY	3c
132	TREATMENT FAILURE	4b
133	COMPLETED PATIENT	1
134	COMPLETED PATIENT	1
135	TREATMENT FAILURE	4a
136	COMPLETED PATIENT	1
137	COMPLETED PATIENT	1
138	COMPLETED PATIENT	1
139	COMPLETED PATIENT	1
140	COMPLETED PATIENT	1
141	COMPLETED PATIENT	1
142	COMPLETED PATIENT	1
143	TREATMENT FAILURE	4b
144	TREATMENT FAILURE	4a

1-Patient completed all 3 visits and has data from 3 KOH+3 culture results
2a- Patient came for Visit 1 only. 2b- Patient came for Visits 1+2 only
2c- Missing KOH/culture at any visit. 2d- Came too late for Visit 2 or 3
3a- Protocol violation (inc/exc) 3b- Asymptomatic at Visit 1
3c- Negative KOH/culture at Visit 1 4a- Positive KOH/culture at Visit 2
4b- Positive KOH/culture at Visit 3 5-Patient withdrew from study due to ADR

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
Subject classification list

Subject	Class	Code
145	COMPLETED PATIENT	1
146	TREATMENT FAILURE	4b
147	COMPLETED PATIENT	1
148	COMPLETED PATIENT	1
149	COMPLETED PATIENT	1
150	COMPLETED PATIENT	1
151	COMPLETED PATIENT	1
152	COMPLETED PATIENT	1
153	LOST TO FOLLOW-UP OR MISSING DATA	2d
154	LOST TO FOLLOW-UP OR MISSING DATA	2d
155	NOT ELIGIBLE FOR STUDY	3c
156	COMPLETED PATIENT	1
157	TREATMENT FAILURE	4b
158	COMPLETED PATIENT	1
159	COMPLETED PATIENT	1
160	COMPLETED PATIENT	1
161	TREATMENT FAILURE	4b
163	TREATMENT FAILURE	4b
164	COMPLETED PATIENT	1
165	COMPLETED PATIENT	1
166	COMPLETED PATIENT	1
168	COMPLETED PATIENT	1
169	NOT ELIGIBLE FOR STUDY	3c
170	NOT ELIGIBLE FOR STUDY	3c
171	COMPLETED PATIENT	1
172	TREATMENT FAILURE	4b
173	COMPLETED PATIENT	1
174	LOST TO FOLLOW-UP OR MISSING DATA	2a
175	NOT ELIGIBLE FOR STUDY	3c
176	TREATMENT FAILURE	4b

N = 159

1-Patient completed all 3 visits and has data from 3 KOH+3 culture results
2a- Patient came for Visit 1 only. 2b- Patient came for Visits 1+2 only
2c- Missing KOH/culture at any visit. 2d- Came too late for Visit 2 or 3
3a- Protocol violation (inc/exc) 3b- Asymptomatic at Visit 1
3c- Negative KOH/culture at Visit 1 4a- Positive KOH/culture at Visit 2
4b- Positive KOH/culture at Visit 3 5-Patient withdrew from study due to ADR

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

Project Number 901368

Investigator Summary Table

Investigator Name	Specialty	# Pt. entered / # Pt. evaluable
[redacted]	Ob/Gyn	29 / 28
[redacted]	Ob/Gyn	3 / 1
[redacted]	G.P.	17 / 13
[redacted]	Ob/Gyn	27 / 18
[redacted]	Ob/Gyn	26 / 25
[redacted]	G.P.	4 / 2
[redacted]	Ob/Gyn	24 / 16
[redacted]	Ob/Gyn	28 / 26
[redacted]	G.P.	1 / 1
Total	9	159 / 130

APPEARS THIS WAY
ON ORIGINAL

Report Investigator Summary (Table 4/summary.dat) created on 17/05/95.

1.6 "Pooling" of Data Across Study Centres

There were large discrepancies between the actual sample size contribution from each centre. In general, the contributions from each centre were not balanced. The sample size ranged from a low of 1/130 (0.9%) from [redacted] to a high of 27/130 (20.8%) for [redacted]

For the purpose of this analysis, study centres contributing less than 10 subjects were themselves pooled to form a comparison group labelled as "Others".

Investigator	Miconazole (Perrigo)	Monistat-7 (Ortho)	Total patients	
[redacted]	13	14	27	20.8%
	1	0	1	0.8%
	6	7	13	10.0%
	10	9	19	14.6%
	14	11	25	19.2%
	1	1	2	1.5%
	9	7	16	12.3%
	14	12	26	20.0%
	0	1	1	0.8%
[redacted]	68 (52.3%)	62 (47.7%)	130	100.0%

The demographic and background information in general did differ significantly across the study centres for age ($p=0.01$), but not for weight ($p=0.15$) nor for height ($p=0.59$). Previous Treatment for VCI ($p<0.0005$) and Treatment Response for Previous VCI ($p<0.0005$) were also statistically significant.

These inter-investigator differences which were statistically significant were not considered to be of any clinical significance which could preclude the pooling of data across study centres. There were no statistically significant differences in other demographic or presentation characteristics.

There were no statistically significant differences for mycological ($p=0.91$) or clinical cure ($p=0.67$) or combined mycological/clinical cure ($p=0.93$) as determined by Chi-square analysis or Rank sums (Kruskal-Wallis) tests.

Prepared by: [redacted] Date : Monday

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

Project Number 901368

Subject, Treatment and Classification Distribution

Investigator	Subject	Initials	Treatment	Code
	1	L-GAG	Perrigo	1
	2	C-DIO	Perrigo	4b
	3	V-LIM	Ortho	1
	4	S-CIC	Ortho	1
	5	J-VEI	Ortho	1
	6	D-GAG	Perrigo	1
	7	L-BUR	Ortho	1
	8	L-GEL	Perrigo	1
	9	C-GUE	Perrigo	5
	10	A-PER	Ortho	1
	11	S-SIM	Perrigo	4a
	12	J-LAR	Ortho	1
	13	A-BRA	Ortho	1
	14	C-GAL	Perrigo	1
	15	C-DUB	Ortho	4a
	16	A-STA	Perrigo	1
	17	M-PAR	Ortho	1
	18	D-LAB	Ortho	1
	19	L-LAU	Perrigo	1
	20	S-SAB	Perrigo	4a
	59	N-LEF	Ortho	1
	60	L-JOL	Perrigo	1
	61	I-SAR	Ortho	1
	62	V-EMO	Ortho	4b
	63	S-GRA	Perrigo	1
	64	P-KIM	Perrigo	1
	65	L-SAB	Ortho	4b
	66	D-GRA	Perrigo	4b
Total subjects for		28		

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

	BASELINE			1ST REVISIT				2ND REVISIT					
	Treatment=Perrigo												
Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
1 MANSOUR	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	Moderate	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	Severe	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	39
20 "	Pos	Pos	Mild	Neg	Pos	None	14	.	.	.	No	No	.
22 FRYMAN	Pos	Pos	Moderate	Neg	Pos	None	28	.	.	.	No	No	.
29 GOUCHA	Pos	Pos	Moderate	Neg	Neg	None	18	Neg	Neg	None	Yes	Yes	42
30 "	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
36 "	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	None	No	Yes	38
37 "	Pos	Pos	Moderate	Neg	Neg	None	14	Neg	Pos	None	No	Yes	43
39 "	Pos	Pos	Moderate	Neg	Neg	None	15	Pos	Pos	Mild	No	No	42
42 SIDAUI	Pos	Pos	Mild	Neg	Neg	Mild	23	Neg	Neg	None	Yes	Yes	36
44 "	Pos	Pos	Mild	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	45
45 "	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	42
47 "	Pos	Pos	Mild	Neg	Neg	Mild	22	Neg	Neg	Mild	Yes	No	47
50 "	Pos	Pos	Moderate	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
51 GOUACH	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
60 MANSOUR	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
63 "	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
64 "	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
66 "	Pos	Pos	Severe	Neg	Pos	None	14	Neg	Pos	None	No	Yes	36
69 - RYOU	Pos	Pos	Severe	Neg	Neg	None	20	.	.	.	No	No	.
74 "	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Neg	None	Yes	Yes	41
79 "	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	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

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						
Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
3 MADISON	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	42
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	.	.	.	No	Yes	37
17 "	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Neg	None	Yes	Yes	36
18 "	Pos	Pos	Moderate	Neg	Neg	None	17	Neg	Neg	None	Yes	Yes	39
23 MAHOUR	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
24 "	Pos	Pos	Moderate	Pos	Pos	Mild	15	.	.	.	No	No	50
25 "	Pos	Pos	Moderate	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	43
32 GOUGEON	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	17	Neg	Neg	None	Yes	Yes	42
40 "	Pos	Pos	Moderate	Neg	Neg	None	12	Pos	Pos	Mild	No	No	40
41 SIDANI	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
43 "	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	Mild	Yes	No	44
46 "	Pos	Pos	Mild	Neg	Neg	None	16	Neg	Neg	None	Yes	Yes	37
48 "	Pos	Pos	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	44
52 Gouak	Pos	Pos	Moderate	Pos	Pos	Moderate	20	.	.	.	No	No	.
53 "	Pos	Pos	Mild	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	36
59 KONSOUR	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	38
61 "	Pos	Pos	Severe	Neg	Neg	None	15	Neg	Neg	None	Yes	Yes	37
62 "	Pos	Pos	Severe	Neg	Neg	None	17	Neg	Pos	None	No	Yes	39
65 "	Pos	Pos	Severe	Neg	Neg	None	20	Neg	Pos	None	No	Yes	43
72 LAVOIE	Pos	Pos	Severe	Neg	Neg	None	14	Neg	Pos	None	No	Yes	42
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

* 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 ineligible 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*
Treatment=Perrigo													
9	Pos	Pos	Severe	n/d	n/d	Moderate	15	Pos	n/d	Moderate	No	No	36
21	Pos	Neg	Severe	Neg	Neg	Moderate	15				No	No	
27	Pos	Pos	Moderate	Neg	Neg	None	17					No	
35	Pos	Pos	Severe	Neg	Neg	None	15				No	No	
54	Pos	Pos	Moderate	Neg	Neg	Mild	15				No	No	
55	Pos	Pos	Mild									No	
68	Pos	Pos	Severe	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	43
70	Pos	Pos	Severe	Neg	Neg	None						No	
73	Pos	Neg	Severe									No	
78	Pos	Neg	Moderate										
109	Pos	Neg	Mild										
154	Pos	Pos	Moderate	Neg	Neg	None							
170	Pos	Neg	Moderate										
174	Pos	Pos	Moderate										

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 ineligible patients, by treatment group

	BASELINE			1ST REVISIT				2ND REVISIT					
	Treatment=Ortho												
Subject	KOH	CULT	Symptoms	KOH	CULT	Symptoms	#Days*	KOH	CULT	Symptoms	Mycol cure	Clin cure	#Days*
26	Pos	Neg	Moderate	.	.	.	.	.	.	.	.	No	.
31	Pos	Pos	Mild	.	.	.	.	.	.	.	.	No	.
49	Pos	Pos	Mild	Neg	Neg	Moderate	15	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	20	Neg	Neg	None	Yes	Yes	42
131	Pos	Neg	Mild	Neg	Neg	None	22	Neg	Neg	None	Yes	Yes	45
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

Came too late for Visit 2 or 3	77, 90, 153, 154

A total of 130 patients were considered to be eligible for analysis of mycological and clinical cure rate. This includes patients with the following minor protocol deviations:

Missing diary:	22, 34, 40, 98, 104
Missing Pregnancy Tests:	76, 93, 112, 121, 122, 123, 124, 126, 127, 129, 130, 132, 133, 139, 140, 142, 144, 148
Eight days between sample date and first day of treatment	42, 43, 95, 164, 168

Patient Numbers 14 and 141 were under age to participate in this study, but their parents co-signed the consent form.

All analyzed patients were within 2 days early to 7 days late for Visit 2.

At Visit 3 all patients were within a week of their scheduled visit, with the following exceptions:

	Patient No.
09 days late:	152
16 days late:	151

The Intent-to-Treat analysis included 159 patients.

Demographic Data:

68 patients were included in the Perrigo group and 62 patients in the Ortho group. There was no statistically significant difference between the two groups ($p > 0.05$) in weight, height and age.

Mycological Cure Rate:

All patients included in the mycological cure rate analysis had a positive KOH and culture at Visit 1.

Mycological cure, defined as KOH and culture results negative at both Visit 2 and Visit 3, was reported for 73.53% (50/68) of the Perrigo group and 77.42% (48/62) of the Ortho group (Table 2a). Comparison of the two active treatments showed no statistically significant difference ($p = 0.756$; 90% C.I.: -17.83% to 10.05%).

Individual Visit 2 and Visit 3 mycological cure rate data are shown in Table 2b.

APPEARS THIS WAY
ON ORIGINAL

At each patient visit the physician was asked to record the severity of the clinical signs and symptoms according to a 0-3 severity of symptoms rating scale.

Any adverse event experienced by the patient, or noticed by the physician, was reported on an adverse event form.

CRITERIA FOR CLINICAL AND MYCOLOGICAL CURE:

"Mycological cure" was considered to be negative KOH and culture at both Visits 2 and 3. "Clinical cure" was defined as an improvement of symptoms at Visit 2 (compared to Visit 1) and absence of symptoms at Visit 3.

Pertaining to the "Clinical Cure" definition, after meeting with the FDA on February 8, 1993, the definition was changed from the one indicated in the protocol to the one in the above paragraph. All statistical analyses were done according to the approved FDA definition.

"Overall cure" was defined as a combination of both mycological cure and clinical cure, as described above. Any patient who had a positive culture or KOH at either Visit 2 or Visit 3, or an exacerbation of symptoms, was considered not cured (i.e. "fail").

STATISTICAL ANALYSIS:

Statistical calculations and data tabulation were performed using SAS for microcomputers, Version 6.04, (SAS, Statistical Analysis System, Cary, N.C., 1989.). Significance levels for Student-t test, Chi-square or adjusted Chi-square test, Wilcoxon Ranks Sums test and the Kruskal-Wallis test were based on the 5% alpha-level.

Confidence interval and power calculations were based on the method defined by J.L. Fleiss (Statistical Methods for Rates and Proportions. 2nd Edition, J.L. Fleiss, John Wiley and Sons N.Y. pp 29-30).

RESULTS:

Subject Classification:

APPEARS THIS WAY
ON ORIGINAL

A total of 159 patients were entered into the study. Of these, 29 were not analyzed for the following reasons:

Reason for exclusion from efficacy analysis	Pat. No.
Negative first culture :	21, 26, 71, 73, 78, 86, 107, 109, 125, 131, 155, 169, 170, 175
Drop out from AER:	9
Protocol Violation:	49
Lost to follow up or missing data:	
Visit for Visit 1 only	27, 31, 55, 67, 174
Visit for Visit 1 and 2 only	35, 54, 68, 70

August 29, 1995

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

PROTOCOL 901368

Visit Specific Mycological Cure Rates

	No. of Patients/Total No. of Evaluable Patients (%)	
Treatment Group	Mycological Cure Visit 2	Mycological Cure Visit 3
Perrigo	62/68 (91.18%)	50/63 - (79.37%)
Ortho	58/62 (93.55%)	48/60 (80.00%)
p-value	0.612	0.930

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

August 28, 1995

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

PROTOCOL 901368

Clinical Cure Rates

	No. of Patients/Total No. of Evaluable Patients (%)	
Treatment Group	Improvement of Symptoms Visit 2	No symptoms Visit 3
Perrigo	68/68 (100%)	55/64 (85.94%)
Ortho	61/62 (98.39%)	56/60 (93.33%)
p-value	N/A	0.179

Project No. 901368

Table 4

Overall Combined Mycological and Clinical Cure Rate*

Number of patients classified as Overall Cure (% of patients)			
Perrigo	Ortho	p-value	90% C.I. (%
48/68 (70.59%)	47/62 (75.81%)	0.637	-19.51 to 9.08

* Overall Cure is defined as mycological cure and clinical cure

APPEARS THIS WAY
ON ORIGINAL

Results:

Table 1

PATIENTS EVALUABLE AT 1ST REVISIT

BY APPLICANT n = 159

INVESTIGATOR:

	Perrigo	Ortho	Total
	# Pt. Entered/ # Pt. Evaluable		
[redacted]	(OB-GYN)		28/18
	(OB-GYN)		28/26
	(OB-GYN)		28/28
	(OB-GYN)		26/25
	(OB-GYN)		24/16
	(G.P.)		17/13
	(G.P.)		4/2
	(OB-GYN)		3/1
	(G.P.)		1/1
	Total		159/130

Project No. 901368

Table 1

Demographic Data

	Test: Perrigo (n = 68)	Reference: Ortho (n = 62)
Mean weight (kg)	60.8	59.6
(range)	(44.5 - 109.1)	(45.4 - 86.4)
Mean height (cm)	162.8	160.5
(range)	(152.0 - 182.8)	(139.7 - 180.0)
Mean age (years)	31.2	32.0
(range)	(16.2 - 62.9)	(14.5 - 65.1)

Project No. 901368

Table 2a

Mycological Cure Rate

Number of patients with mycological cure* (% of patients)			
Perrigo	Ortho	p	C.I.
50/68 (73.53%)	48/62 (77.42%)	0.756	-17.83 to 10.05%

p value = between treatment groups
C.I. = 90% confidence intervals for the difference between cure rates

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

Table 2b

KOH and Culture Cure Rates at Visit 2 and Visit 3

Number of patients with results negative (% of patients)				
	Visit 2		Visit 3	
Treatment Group	KOH	Culture	KOH	Culture
Perrigo	67/68 (98.53%)	62/68 (91.18%)	55/63 (87.30%)	51/63 (80.95%)
Ortho	58/62 (93.55%)	59/62 (95.16%)	56/60 (93.33%)	48/60 (80.00%)
p-value:	0.308	0.584	0.411	1.000
90% C.I.(%):	-2.23 to 12.19	-12.74 to 4.78	-16.36 to 4.29	-12.44 to 14.34

p value = between treatment groups
C.I. = 90% confidence intervals for the difference between cure rates

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

ADMINISTRATIVE DOCUMENTS

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

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

(TITLE 21, Code of Federal Regulations, 314)

Form approved : OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

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

NAME OF APPLICANT **L. Perrigo Company**	DATE OF SUBMISSION **April 14, 1997**
ADDRESS *(Number, Street, City, State, and Zip Code)* **117 Water Street** **Allegan, MI 49010**	TELEPHONE NO. (Include Area Code) **(616) 673-8451**
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* **ANDA 74-760**

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
Miconazole Nitrate Cream	

CODE NAME (If any)	CHEMICAL NAME
	Miconazole Nitrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Cream	**Vaginal**	**2%** **100 mg per dose**

PROPOSED INDICATIONS FOR USE

For the treatment of vaginal yeast infections (candidiasis)

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

1. **L. Perrigo Company**
   ANDA #74-760

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

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

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

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Monistat ®7	**R. W. Johnson**

TYPE SUBMISSION *(Check one)*

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

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) **21 CFR 314.120**

PROPOSED MARKETING STATUS *(Check one)*

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

CONTENTS OF APPLICATION

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

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

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

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

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

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
David A. Jespersen, Director, Technical Services	David A Jespersen	4/14/97

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. *(Include Area Code)*
117 Water Street **Allegan, MI 49010**	(616) 673-8451

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

Redacted 2

pages of

trade secret and/or

confidential

commercial

information

APPROVAL PACKAGE SUMMARY FOR 74-760

ANDA: 74-760

FIRM: L. Perrigo Company

DRUG: Miconazole Nitrate

APPEARS THIS WAY
ON ORIGINAL

DOSAGE: Cream

STRENGTH: 2%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 4/7/97

BIO STUDY/BIOEQUIVALENCE STATUS: The comparative clinical study has been found acceptable by the Division of Anti-Infective Drug products, and by the Division of Bioequivalence 3/6/97.

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has submitted satisfactory three months accelerated stability data at 40°C/75%RH and 12 months room temperature stability data at 25-30°C.

LABELING REVIEW STATUS: Labeling is satisfactory by L. Golson 10/16/96

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted a copy of the executed batch record batch # 4BH172 for ——
The firm has provided copies of the master formula and manufacturing procedures for the intended production batches for —— and ——
The firm will be using the same drug substance manufacturer ——
DMF —— The DMF is satisfactory, same manufacturing procedures and same equipments.

COMMENTS: The Application is APPROVABLE.

/S/ 4/16/97

REVIEWER: Nashed E. Nashed, P.D. DATE: 4/16/97

SUPERVISOR: Paul Schwartz, Ph.D.

/S/ 4/16/97

CDER Establishment Evaluation Report
for April 10, 1997

Application: ANDA [redacted]760/000
Stamp: 02-OCT-1995 Regulatory Due:
Applicant: L PERRIGO
117 WATER ST
ALLEGAN, MI 49010

Priority:
Org Code: 600
Action Goal:
District Goal: 02-DEC-1996
Brand Name:
Established Name: MICONAZOLE NITRATE
Generic Name:
Dosage Form: CRM (CREAM)
Strength: 2% VAGINAL

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 07-APR-1997 by M. EGAS (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No: [redacted]

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATI 02-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

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

DMF No:

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDATI 02-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATI 07-APR-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

Reference is made to Perrigo's August 9, 1996 amendment. On page 7, the sponsor says that total impurities will not be more than — including the ordinary impurities.

However, the specification listed under the certificate of analysis on page 9 does not clearly state the — limit for **total impurities including ordinary impurities**.

Ms. Green was asked to revise page 9 accordingly.

She said Perrigo would comply.

cc:
ANDA
Division File
T-con Binder

DATE
4/14/97

ANDA NUMBER
74-760

IND NUMBER

TELECON

INITIATED BY FDA

PRODUCT NAME
Miconazole Nitrate Vaginal Cream, 2%

FIRM NAME
Perrigo

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Virginia Green

TELEPHONE NUMBER
616-673-7604

SIGNATURE
Joseph Buccine

/S/ 4/14/97

APPEARS THIS WAY
ON ORIGINAL

2.1

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

REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
-520 Dr. Julius Piver		HFD-650 -- Division of Bioequivalence	
DATE: 4/9/96	IND NO.	NDA NO. N 74-760	TYPE OF DOCUMENT: Study Amendment
DATE OF DOCUMENT: 3/20/96	NAME OF DRUG: Miconazole Nitrate	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG
DESIRED COMPLETION DATE: 60 Days	NAME OF FIRM: L. Perrigo		

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

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

Enclosed are the reformatted data tables requested in your FAX to the sponsor dated 2/16/96.

Please enclose with you review, a copy of the review on diskette, or the file name and Lan location of the file so our reviewer can access the text.

Please return to Generic Drugs Document Room --Metro Park North II Room E150
Deliver ot Larry Galvin Room E118 -- Any Questions Call at 4-2290

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

FORM FDA 3291 (7/83)

Redacted _____

pages of trade secret and/or confidential commercial information

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

REQUEST FOR CONSULTATION

P.M. 11/18/96

TO (Division/Office) 4 -- HFD-~~105~~ 104 (~~Mary Jane Walling~~) Toni Nearing RD			FROM: HFD-650 -- Division of Bioequivalence	
11/15/96	IND NO.	NDA NO. N 74-760	TYPE OF DOCUMENT	DATE OF DOCUMENT 10/29/96
NAME OF DRUG Miconazole Nitrate		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE ASAP
NAME OF FIRM Perrigo				

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER

III. BIOPHARMACEUTICS

- ISSOLUTION
- OAVAILABILITY STUDIES
- HASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL— BIOPHARMACEUTICS
- ☐ IN—VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

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

For review by Dr. Ali Vasatos HFD-520.

This consult consists of a manila folder including a 43 page response to our request for information in a letter dated October 8, 1996.

Please include, with you review, a copy of the review text on computer diskette, or, the file name and LAN location of the file, so our reviewer can access the text. Thanks!!

11/25/96 To Lesser for assignment, AS

MPN II HFD 612

ase return to Generic Drugs Document Room -- Metro Park North 2 - Room E150.
Deliver to Larry Galvin -- Room E118. Any questions Please call Larry at 4-2290

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

FORM FDA 3291 (7/83)

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

CRP(5220)

REQUEST FOR CONSULTATION

RECEIVED

TO (Division/Office)		FROM:
HFD 520 ODE 5 - ~~HFD-105~~ ~~Mary Jane Walling~~		HFD-650 Division of Bioequivalence
DATE: 10/30/96	IND NO.	NDA NO.: N 74-760
TYPE OF DOCUMENT	DATE OF DOCUMENT: 10/1&4/	
NAME OF DRUG: Miconazole Nitrate	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG
DESIRED COMPLETION DATE: ASAP		

NAME OF FIRM: Perrigo

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

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

For review by Dr. Ali Vasatos HFD

This consult consists of two submissions of 6 and 5 pages, respectively, together in a manila folder.

When you review is complete, please include either a computer diskette with your review on it, or the file name and LAN location of the file so our reviewer can access the text.

Thank you for you assistance.

Please return the consult to the Generic Drugs Document Room--Metro Park North 2 Rm E150. Deliver to Larry Galvin Room E118.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND
ATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

11/19/96 To Brad Leissa for assignment—9 Bons

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

Date: 13-Nov-1996 01:18pm EST
From: Mary Jane Walling
WALLINGMA
Dept: HFD-105 CRP2 S220
Tel No: 301-827-2268 FAX 301-827-2317

TO: Laurence Galvin (GALVIN)

Subject: ANDA 74-760

this application does not belong to ODE V. It belongs in 520 ODE IV because it is a vaginal indication

I have given it to Toni Nearing in HFD 104

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 74-760

Date of Submission:
October 16, 1996 (Amendment)

Applicant's Name: L. Perrigo Company

Established Name: Miconazole Nitrate Vaginal Cream, 2%

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: (45 g tube)
Satisfactory as of August 9, 1996 submission

Carton Labeling: (1 reusable applicator)
(7 disposable applicators)

Satisfactory as of August 9, 1996 submission

Patient Package Insert Labeling:
Satisfactory as of October 16, 1996 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: #17-450

NDA Drug Name: Miconazole Nitrate Vaginal Cream, 2%

NDA Firm: Advanced Care Products

Date of Approval of NDA Insert and supplement #040: 2/9/95
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: 17-450
Basis of Approval for the Carton Labeling: 17-450

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 23, Supplement 6 and product has not been proposed for the PF.**		x	
Is this name different than that used in the Orange Book?		x	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
PACKAGING **The applicant is proposing two packaging configurations, one 45 g tube with one reusable applicator or 7 disposable applicators**			
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	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? **Package insert (EDUCATIONAL BROCHURE) should accompany the product. The carton is needed to store the reusable tube of cream and it applicator(s).**			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? **Contrasting colors are being used for the one applicator and 7 applicators cartons.**		X	

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? **Contrasting colors are being used for the one applicator and 7 applicators cartons.**		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed) Page 98, Volume 1.1			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) **NDA - Store at room temperature, 15°-30°C (59°-86°F). Avoid heat over 30°C or 86°F.** **ANDA - Same as innovator**			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) **Results pending.**			x
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **None pending.**			

February 6, 1996 to also include the option of marketing with 7 disposable applicators.

3. Perrigo has included the statement "Compare to Monistat® 7's active ingredient" on the carton which is acceptable language when a generic firm wants to compare its product with the RLD on its labeling.

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

Date of Review:
12/17/96

Date of Submission:
10/16/96

Primary Reviewer:
/S/

Date:
12/30/96

Secondary Reviewer:
/S/

Date:
12/30/96

Team Leader:
/S/

Date:
12/30/96

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cc: ANDA: 74-760
DUP/DIVISION FILE
HFD-613/LGolson/CHoppes/JGrace (no cc)
njg/12/20/96/x:\new\firmsnz\perrigo\ltrs&rev\74760ap.1
Review

APPEARS THIS WAY
ON ORIGINAL

2-1

DATE: SEP 23 1996

TO: Director, Detroit District, HFR-MW200

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

SUBJ: Top 200 Inspection Request
ANDA 74-760, Miconazole Nitrate Vaginal Cream 2%

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

PROFILE: OIN

REVIEWER: W. Russell
TELEPHONE: 301-594-1841

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

CFN#: 1811666

In connection with FDA's review of **ANDA 74-760**, please conduct an inspection of the above referenced establishment. The application provides for this establishment to **manufacture and test** the above listed product. This is a **Top 200 Drug Product**, requiring a product specific inspection regardless of the last GMP EI covering the profile class **OIN**. 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.

Please send withhold and approval answers in the prescribed format via facsimile (FAX) 301-827-0145, or EMS, as soon as possible after the completion of the inspection, before the report write up starts. If classified OAI, recommend withhold and provide complete establishment inspection report with exhibits documenting deficiencies to HFD-324 **within 30 days**. If NAI recommend approval via EMS and forward endorsement (FD-481(E)-CG) by mail.

In communicating with this office (FTS 301-827-0062), reference should be made to **ANDA 74-760**. Please direct your written response to the Investigations & Compliance Evaluation Branch, HFD-324.

/s/

for Mark A. Lynch

Priority: **ANDA pending**
Target Completion: OCT 23 1996

cc:
HFD-324 ICEB R/F
HFD-324 EER File
HFD-629 RUSSELL/NASHED
9/17/96:VSP
a:PERRIGO.WATER.200

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: 25-Sep-1996 11:20am EDT
From: Melvin Robinson
MROBINSO@FDAEM@SSWMBX@FDAOC
Dept:
Tel No:

TO: GHARTLAG@FDAEM@SSWMBX@FDAOC

CC: FERGUSONS@A1@FDACD
CC: RUSSELLW@A1@FDACD
CC: GDOMINGO@FDAEM@SSWMBX@FDAOC

Subject: 74-760

TO:*Gretchen Hartlage, CSO, Grand Rapids Resident Post

CC:*William Russell, Reviewer, HFD-629
*George Domingo, Det-Do Drug Team Leader
*Shirnette Ferguson, HFD-324

SUBJ:*ANDA 74-760, PAI Request

*Melvin O. Robinson, PAI Manager, Det-Dp

PRDT:*Miconazole Nitrate Vaginal Cream, 2%,
PROFILE: OIN

FIRM:*Perrigo Co.
*117 Water Street
*Allegan, MI 49010
*CF# 1811666

This is to acknowledge receipt of the HFD-324 inspection request memo dated September 23, 1996. A copy is being sent to Grand Rapids today.

Gretchen: I cannot find any Field Copy in the Detroit Office on this NADA, but there is a card in ——— Card File indicating we had something about the application. Maybe it is one that I handed to you a couple of weeks ago. *I put this into WATS with a 3/31/97 Due Date so I could give it a B priority. That is because there is not a User-Fee involved. We already have another Priority B PAI pending for an Ibuprofen liquid product with a due date of 2/28/97. Both should be conducted at the same time, with GMP coverage of those two profile classes.

I informed HFD-324 recently that the firm was scheduled for December 1996, and we expect to do them for ——— GMP's after January 1st.

The current profile shows OIN as inactive, while ~ is due for two years the end of February.

2.1

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

Date of Review: September 17, 1996 (Minor Amendment)

ANDA Number: 74-760 Review Cycle: #2 (Draft and FPL)

Date of Submission: August 9, 1996

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

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

Proprietary Name: None

Established Name: Miconazole Nitrate Vaginal Cream, 2%

Reviewer: Lillie D. Golson

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

Telephoned Dawn Breed and requested FPL for insert labeling. 9/20/96

1. CONTAINER (45 g tube)

   Satisfactory

2. CARTON (1 reusable applicator)
   (7 disposable applicators)

   Satisfactory

3. INSERT

   Satisfactory in draft. Prepare and submit final printed patient package insert labeling.

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23, Supplement 6 and product has not been proposed for the PF.		x	
Is this name different than that used in the Orange Book?		x	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
PACKAGING **The applicant is proposing two packaging configurations, one 45 g tube with one reusable applicator or 7 disposable applicators**			
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	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? **Package insert (EDUCATIONAL BROCHURE) should accompany the product. The carton is needed to store the reusable tube of cream and it applicator(s).**			
Are there any other safety concerns?		x	
LABELING			

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? Package insert (EDUCATIONAL BROCHURE) should accompany the product. The carton is needed to store the reusable tube of cream and it applicator(s).			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? Contrasting colors are being used for the one applicator and 7 applicators cartons.		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed) Page 98, Volume 1.1			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) NDA - Store at room temperature, 15°-30°C (59°-86°F). Avoid heat over 30°C or 86°F. ANDA - Same as innovator			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	

FOR THE RECORD:

1. **Labeling review based on Advanced Care Product's labeling approved 2/9/95 for Monistat® 7 Vaginal Cream.**

2. **Applicant's original application only included one reusable applicator; however, Perrigo amended this application February 6, 1996 to also include the option of marketing with 7 disposable applicators.**

3. **Perrigo has included the statement "Compare to Monistat® 7's active ingredient" on the carton which is acceptable language when a generic firm wants to compare its product with the RLD on its labeling.**

4. **Perrigo submitted printer's proof as FPL. Since this is a minor amendment, firm will be telephoned regarding FPL for their package insert labeling. Firm will also be asked to try to enhance the illustrations on their disposable insert.**

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

/S/ 9/20/96
Primary Reviewer Date

/S/ 9/20/96
Secondary Reviewer Date

/S/ 9/20/96
John Grace Date
Acting Team Leader, Labeling Review Branch

cc: ANDA 74-760
HFD 613/LGolson/CHoppes/JGrace
HFD 627 Nashed Nashed
Dup
Division File

see x:/new/firmsnz/perrigo/ltrs&rev/74760na2.l

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

Date of Review: August 27, 1996 Date of Submission: Aug. 9, 1996

Primary Reviewer: Charlie Hoppes

Secondary Reviewer: John Grace

ANDA Number: 74-760 **Review Cycle: #2**

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

Manufacturer's Name (If different than applicant):

Proprietary Name: None

Established Name: Miconazole Nitrate Vaginal Cream, 2%

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

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER (45 g tube)

   On the principal display panel, it is unnecessary for the established name to appear twice. You may delete the smaller printed established name, and increase the prominence of "2%".

2. CARTON (1 reusable applicator)
   (7 disposable applicators)

   Main display panel: See CONTAINER comment.

3. EDUCATIONAL BROCHURE (1 reusable applicator)

   Satisfactory in draft. (7 disposable applicators)

   Revise your package insert labeling, as instructed above, and submit the container labels, carton and insert labeling in final print.

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23, Supplement 6 and product is not been proposed for the PF.		X	
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
PACKAGING The applicant is proposing two packaging configurations, one 45 g tube with one reusable applicator or 7 disposable applicators			
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	
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 strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? Package insert (EDUCATIONAL BROCHURE) should accompany the product. The carton is needed to store the reusable tube of cream and it applicator(s).			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? Contrasting colors are being used for the one applicator and 7 applicators cartons.		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed) Page 98, Volume 1.1			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) NDA - Store at room temperature, 15°-30°C (59°-86°F). Avoid heat over 30°C or 86°F. ANDA - Same as innovator			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	

Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) Results pending.			x
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. None pending.			

NOTE TO CHEMIST:

Please notify Labeling Reviewer if there are no chemistry deficiencies. If this is the case, since the application is in Minor Amendment status, we will notify the firm of the labeling deficiencies by telecon.

FOR THE RECORD:

1. **Labeling review based on Advanced Care Product's labeling approved 2/9/95 for Monistat® 7 Vaginal Cream.**

2. **Applicant's original application only included one reusable applicator; however, Perrigo amended this application February 6, 1996 to also include the option of marketing with 7 disposable applicators.**

3. **Perrigo has included the statement "Compare to Monistat® 7's active ingredient" on the carton which is acceptable language when a generic firm wants to compare its product with the RLD on its labeling.**

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

/S/

Primary Reviewer

7/5/96

Date

/S/

Acting Team Leader
Labeling Review Branch

7/5/96

Date

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

Date of Review:
May 10, 1996

Date of Submission:
December 22, 1995 (original)
January 31, 1996 (amendment)

Primary Reviewer: **Lillie D. Golson**

Secondary Reviewer: **John Grace**

ANDA Number: **74-760** **Review Cycle: #1**

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

Manufacturer's Name (If different than applicant):

Proprietary Name: **None**

Established Name: **Miconazole Nitrate Vaginal Cream, 2%**

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

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER (45 g tube)

   Revise your expression of strength to read, "Miconazole Nitrate Vaginal Cream, 2%".

2. CARTON (1 reusable applicator)
   (7 disposable applicators)

   See CONTAINER comment.

3. EDUCATIONAL BROCHURE

   a. See CONTAINER comment

   b. Directions for Use

      Revise to include the following step and accompanying drawing:

After each use, replace cap and roll tube from bottom (as shown).

(Please note: Neither the text nor the drawing are included in your December 22, 1995 submission; however, the drawing but not the text is included in your January 31, 1996 submission.)

Revise your package insert labeling, as instructed above, and submit the container labels, carton and insert labeling in final print. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23, Supplement 6 and product is not been proposed for the PF.		x	
Is this name different than that used in the Orange Book?		x	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
PACKAGING The applicant is proposing two packaging configurations, one 45 g tube with one reusable applicator or 7 disposable applicators			
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	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? Package insert (EDUCATIONAL BROCHURE) should accompany the product. The carton is needed to store the reusable tube of cream and it applicator(s).			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? Contrasting colors are being used for the one applicator and 7 applicators cartons.		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed) Page 98, Volume 1.1			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) NDA - Store at room temperature, 15°-30°C (59°-86°F). Avoid heat over 30°C or 86°F. ANDA - Same as innovator			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	

Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) Results pending.			x
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. None pending.			

FOR THE RECORD:

1. **Labeling review based on Advanced Care Product's labeling approved 2/9/95 for Monistat® 7 Vaginal Cream.**

2. **Applicant's original application only included one reusable applicator; however, Perrigo amended this application February 6, 1996 to also include the option of marketing with 7 disposable applicators.**

3. **Perrigo has included the statement "Compare to Monistat® 7's active ingredient" on the carton which is acceptable language when a generic firm wants to compare its product with the RLD on its labeling.**

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

/S/

Primary Reviewer

5/17/96

Date

Secondary Reviewer

Date

/S/

Chief, Labeling Rev. Branch

5-17-96

Date

cc:

ANDA 74-760na.1

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 3/21/96

NDA NUMBER: 74-760

IND NUMBER:

TELECON/MEETING

INITIATED BY
- ☐ APPLICANT/SPONSOR
- ☑ FDA

MADE
- ☐ BY TELEPHONE
- ☐ IN PERSON

PRODUCT NAME: Microgyn Metrale Vaginal Cream 20%

FIRM NAME: Perrigo

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Ginger Greene

TELEPHONE NO.: 1-616-673-7670

Dr. Priver requested that I phone the firm to determine when they will submit the information that he requested in his letter dated February 8, 1996. He also contacted them by fax on February 15, 1996. Ginger Greene stated that they had collected the requested information and have already submitted it to OBD. She stated that it should arrive this week.

SIGNATURE: /S/

DIVISION: HFD-615

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

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

Division of Anti-Infective Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-520
Rockville, MD 20857

FACSIMILE TRANSMISSION

DATE: 8.24.95 Number of Pages (including cover sheet) 2

TO: Jacqueline M. Eaton, Regulatory Affairs Manager

COMPANY: Perrigo Company

FAX NUMBER: 616 673-7655

MESSAGE: RE: ANDA 74-395

Attached is prototype of information needed for completion of my review.

1. Mycological Cure - need visit specific mycological cure rates -- combined KOH/culture cure rate for each re-visit.

2. Clinical Cure - need visit specific clinical cure rates -- compatible with diagnosis of clinical cure as in the protocol -- also, rate/visit.

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: Dr. Piver

TITLE: Medical Officer

TELEPHONE: 301 443-4280 FAX NUMBER 301-443-5803 2227

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: 01-Oct-1996 05:29pm EDT
From: Mark Anderson
ANDERSONM
Dept: HFD-617 MPN2 113
Tel No: 301-594-0360 FAX 301-594-3839

TO: Regina Alivisatos (ALIVISATOSR)
TO: Brad Leissa (LEISSAB)

Subject: Final concurence with Perrigo Ltr.

Drs. Alivisatos and Leissa,

Sorry to bother you on this again, but just to make sure you are both in agreement, please look over comments 1 and 2 in the letter to make sure they say what you want.

It appears the way comment #1 is now written it may make comment 2 unecessary (we are asking for dates of therapy now in comment 1)?

T nks! Mark

Before HFD-520 is able to complete a substantive review of the data submitted the following additional information is required:

1. Please submit summary information in line form, by center for each patient, to include demographics, date of enrollment, dates of therapy, dates of post-therapy visits and their relationship to the treatment stop date. (this came from Dr. Alivistatos e mail of 10/30 7:54 a.m.)

2. Please provide information describing when each patient self-administered the drug.

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: 02-Oct-1996 07:58am EDT
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-2325

TO: Mark Anderson (ANDERSONM)
TO: Regina Alivisatos (ALIVISATOSR)

Subject: Re: Final concurence with Perrigo Ltr.

Mark,

Comment 2 is different from Comment 1. Comment 1 says we need to know how follow up visits relate to the last day of therapy. This is one issue.

Comment 2 asks for information about the compliance with which patients self-administered the drug. This is a different issue.

The company's response from Comment 2 will help us learn whether the patients received at least 80% of the proscribed 7 day dosing. So, if a [illegible]ent started study drug on 9/1 and stopped on 9/7 (7 days of therapy) but [illegible] self-administered on days 9/1, 9/2, 9/3, and 9/7, this would demonstrate that the patient violated the study protocol dosing requirement, and thus they would be nonevaluable.

Brad
>
>
>
>
>
>
>Drs. Alivisatos and Leissa,
>
>Sorry to bother you on this again, but just to make sure you are both in agreement, please look over comments 1 and 2 in the letter to make sure they say
>what you want.
>
>It appears the way comment #1 is now written it may make comment 2 unecessary
>(we are asking for dates of therapy now in comment 1)?
>
>Thanks! Mark
>
>Before HFD-520 is able to complete a substantive review of the data [illegible]itted for, the following additional information is required:
>
> 1. Please submit summary information in line form, by center

>
dates each patient, to include demographics, date of enrollment,
>
relationship of therapy, dates of post-therapy visits and their
>
Alivistatos e to the treatment stop date. (this came from Dr.
>mail of 10/30 7:54 a.m.)
>
> 2. Please provide information describing when each patient
>
> self-administered the drug.

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

Date: 02-Oct-1996 07:17am EDT
From: Regina Alivisatos
ALIVISATOSR
Dept: HFD-520 CRP2 N-301
Tel No: 301-827-2198

TO: Mark Anderson (ANDERSONM)

CC: Brad Leissa (LEISSAB)

Subject: Re: Final concurence with Perrigo Ltr.

>
>Mark, I think you are right, everything could be combined. I spoke with the company regarding a question I ahd and have documented that conversation in my review.
Basically, they need to verify in wriiten form, what they told me, that is that the revisit dates that they have provided represent the number of days after therapy. Additionally, in order to independently verify these dates, the line listings are necessary with the actual dates.
>

.
>
>Drs. Alivisatos and Leissa,
>
>Sorry to bother you on this again, but just to make sure you are both in
>agreement, please look over comments 1 and 2 in the letter to make sure they say
>what you want.
>
>It appears the way comment #1 is now written it may make comment 2 unecessary
>(we are asking for dates of therapy now in comment 1)?
>
>Thanks! Mark
>
>Before HFD-520 is able to complete a substantive review of the data submitted
>the following additional information is required:
>
> 1. Please submit summary information in line form, by center for
> each patient, to include demographics, date of enrollment, dates
> of therapy, dates of post-therapy visits and their r tionship
> to the treatment stop date. (this came from Dr. Alivistatos e
>mail of 10/30 7:54 a.m.)
>

> 2. Please provide information describing when each patient
> self-administered the drug.
>
I think that this clarifies what I need

Thanks

Regina Alivisatos
7-2199

APPEARS THIS WAY
ON ORIGINAL

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>cc:
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>BIO-LETTER INCOMPLETE
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>Endorsements:
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>DRAFTED MDA
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Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-760/ Orig File, Dup File
Div File
Field Copy
HFD-600/Reading File
HFD-650/MAnderson, CST
HFD-520/RAlivisatos
HFD-520-BLeissa

R.Alivisatos/B.Leissa
S.Nerurkar
M.Anderson

9/29/96

X:\WPFILE\BIO\N74760D3.def

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: 01-Oct-1996 08:00am EDT
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-2325

TO: Regina Alivisatos (ALIVISATOSR)
TO: Mark Anderson (ANDERSONM)

Subject: Re: FWD: Re: Draft Def. Letter for Perrigo 74-760

Mark,

So that you understand, when Dr. Alivisatos refers to our requesting the medication self-administration records, we don't want copies of the actual records. However, we *would* like Perrigo to submit an amendment containing the information describing when patients self-administered the drug. In this way, we can check drug compliance of the patients.

Just wanted to clarify in case there was an ambiguity.

>>Mark,
>
>I am in agrrement with paragraph one.
>>
>>However,I would delete the last paragraph and only have a sentence that
>states that Medication self-administration records are requested.
>
>Because the duration of therapy was 1 week, the example was to
>illustrate that that was what I wanted.
>
>Regina Alivisatos
>7-2199
>>
>>
>>
>>Drs. Alivisatos and Leissa,
>>
>>Thanks for your prompt feedback on the draft letter. Am I right in
>>understanding you are in agreement with original wording for comment 1
>OR do you
>>prefer:
>>
>>Please submit summary information in line form, by center, to include
>>demographics, date of enrollment, dates of therapy, dates of
t-therapy visits
d their relationship to the treatment stop date.
>>
>>Regarding your comment about study taking longer than 1 week
>(10/2-10-9) I

>>wasn't sure what was meant by the E. Mail I got from Dr. Leissa in the
>10/25/96
>>E mail:
>>
>>"Medication self-administration records for all patients (e.g.,
>>10/2/93-10/9/93). Thats why I put those dates in comment 2. Please
>provide a
>>revised comment number 2 for the letter.
>>
>>Thanks, Mark
>>

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: 01-Oct-1996 06:53am EDT
From: Regina Alivisatos
ALIVISATOSR
Dept: HFD-520 CRP2 N-301
Tel No: 301-827-2198

TO: Mark Anderson (ANDERSONM)

CC: Brad Leissa (LEISSAB)

Subject: Re: FWD: Re: Draft Def. Letter for Perrigo 74-760

>Mark,

I am in agrrement with paragraph one.
>
>However,I would delete the last paragraph and only have a sentence that states that Medication self-administration records are requested.

Because the duration of therapy was 1 week, the example was to illustrate that that was what I wanted.

[illegible]na Alivisatos
7-2199
>
>
>
>Drs. Alivisatos and Leissa,
>
>Thanks for your prompt feedback on the draft letter. Am I right in >understanding you are in agreement with original wording for comment 1 OR do you
>prefer:
>
>Please submit summary information in line form, by center, to include >demographics, date of enrollment, dates of therapy, dates of post-therapy visits
>and their relationship to the treatment stop date.
>
>Regarding your comment about study taking longer than 1 week (10/2-10-9) I
>wasn't sure what was meant by the E. Mail I got from Dr. Leissa in the 10/25/96
>E mail:
>
>"Medication self-administration records for all patients (e.g., >10/2/93-10/9/93). Thats why I put those dates in comment 2. Please p[illegible]ide a
[illegible]ised comment number 2 for the letter.
>
>Thanks, Mark
>

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

Date: 30-Sep-1996 04:37pm EDT
From: Mark Anderson
ANDERSONM
Dept: HFD-617 MPN2 113
Tel No: 301-594-0360 FAX 301-594-3839

TO: Regina Alivisatos (ALIVISATOSR)
TO: Brad Leissa (LEISSAB)

Subject: FWD: Re: Draft Def. Letter for Perrigo 74-760

Drs. Alivisatos and Leissa,

Thanks for your prompt feedback on the draft letter. Am I right in understanding you are in agreement with original wording for comment 1 OR do you prefer:

Please submit summary information in line form, by center, to include demographics, date of enrollment, dates of therapy, dates of post-therapy visits and their relationship to the treatment stop date.

I rding your comment about study taking longer than 1 week (10/2-10-9) I w .'t sure what was meant by the E. Mail I got from Dr. Leissa in the 10/25/96 E mail:

"Medication self-administration records for all patients (e.g., 10/2/93-10/9/93). Thats why I put those dates in comment 2. Please provide a revised comment number 2 for the letter.

Thanks, Mark

APPEARS THIS WAY
ON ORIGINAL

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

Date: 30-Sep-1996 07:58am EDT
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-2325

TO: Regina Alivisatos (ALIVISATOSR)
TO: Mark Anderson (ANDERSONM)

Subject: Re: Draft Def. Letter for Perrigo 74-760

Andrea,

The regulations don't allow us to require all CRFs without the Division Director's approval -- where we have strong reason not to trust derived data submitted by the applicant. By law, we are only allowed to *require* CRFs for patients who die or who drop out due to an adverse event.

If Perrigo provides us with the missing datapoints via a linelisting amendment, this should be sufficient.

>>The letter looks fine. However, I would like to phrase it so that it
>reads;: "full case report forms on all enrolled patients, or
>preferably, summary information in line form, by center, to include
>demographics, date of enrollment, dates of therapy, dates of
>post-therapy visits and their relationship to the treatment stop date.
>
>
>I belive that the study took longer than 1 week, i.e. Oct2-Oct.9
>>
>>Thank-you
>
>Regina Alivisatos
>7-2199
>N-343
>>
>>
>>
>>Dr. Alivisatos,
>>
>>Below please find a draft of a letter we prepared to go to Perrigo for
>their
>>Miconazole Vaginal Cream, based on the E. Mail received 9/25/96 from
>Dr. Leissa.
>
ease indicate concurrance via E. Mail or provide corrections.
>>
>>Thanks, Mark Anderson, Project Manager (594-0315)
>>

>>
>>DRAFT:
>>
>>ANDA 74-760
>>
>>
>>
>>L Perrigo Co.
>>Attention: Jacqueline Eaton
>>117 Water Street
>>Allegan, MI 49010
>>
>>
>>Dear Madam:
>>
>>Reference is made to the Abbreviated New Drug Application, submitted on
>
>>September 29, 1995, for Miconazole Nitrate Vaginal Cream.
>>
>>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
llowing comments are provided for your consideration:

>>Before HFD-520 is able to complete a substantive review of the data
>submitted
>>the following additional information is required:
>>
>> 1. Please submit absolute dates (versus relative dates)
>for ALL
>>patient visits (i.e., pre-enrollment screening visit, enrollment visit,
>first
>>post-therapy visit and second post-therapy visit).
>>
>> 2. Please provide medication self-administration records
>for all
>>patients during the study period October 2, 1993 - October 9, 1993).
>>
>> 3. Please provide individual signs and symptoms
>values/scores for
>>all patients at each visit.
>>
>> 4. Please calculate and report a mean clinical symptom
>score at
>>each visit for both study arms for the evaluable population.
>>
>>As described under 21 CFR 314.96 an action which will amend this
>application is
> quired. The amendment will be required to address all of the
ments
>>presented in this letter. Should you have any questions, please call
>Mark
>>Anderson, Project Manager, at (301) 594-0315. In future correspondence

>regarding
>>this issue, please include a copy of this letter.
>>
>>
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>>

Sincerely yours,

/S/

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

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>>cc:
>> ANDA 74-760/ Orig File, Dup File
>> Div File
>> Field Copy
>> HFD-600/Reading File
>> HFD-650/MAnderson, CST
>> HFD-520/RAlivisatos
>> HFD-520-BLeissa
>>
>>
>>BIO-LETTER INCOMPLETE
>>
>>Endorsements:

  R.Alivisatos/B.Leissa
>> S.Nerurkar
>> M.Anderson
>>
>>DRAFTED MDA 9/29/96 X:\WPFILE\BIO\N74760D3.def
>>

I E mailed to 520

ELECTRONIC MAIL MESSAGE

Brad + Regina both read message on 9/30 "Receipt" sent

Date: 29-Sep-1996 02:06pm EDT
From: Mark Anderson
ANDERSONM
Dept: HFD-617 MPN2 113
Tel No: 301-594-0360 FAX 301-594-3839

TO: Regina Alivisatos (ALIVISATOSR)

CC: Brad Leissa (LEISSAB)
CC: Shriniwas Nerurkar (NERURKAR)
CC: Keith Chan (CHANK)
CC: Mark Anderson (ANDERSONM)

Subject: Draft Def. Letter for Perrigo 74-760

Dr. Alivisatos,

Below please find a draft of a letter we prepared to go to Perrigo for their Miconazole Vaginal Cream, based on the E. Mail received 9/25/96 from Dr. Leissa.

Please indicate concurrance via E. Mail or provide corrections.

Thanks, Mark Anderson, Project Manager (594-0315)

DRAFT:

ANDA 74-760

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

Dear Madam:

Reference is made to the Abbreviated New Drug Application, submitted on September 29, 1995, for Miconazole Nitrate Vaginal Cream.

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:

Before HFD-520 is able to complete a substantive review of the data submitted following additional information is required:

1. Please submit absolute dates (versus relative dates) for ALL patient visits (i.e., pre-enrollment screening visit, enrollment visit, first post-therapy visit and second post-therapy visit).

2. Please provide medication self-administration records for all patients during the study period October 2, 1993 - October 9, 1993).

3. Please provide individual signs and symptoms values/scores for all patients at each visit.

4. Please calculate and report a mean clinical symptom score at each visit for both study arms for the evaluable population.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

cc:

ANDA 74-760/ Orig File, Dup File
Div File
Field Copy
HFD-600/Reading File
HFD-650/MAnderson, CST
HFD-520/RAlivisatos
HFD-520-BLeissa

BIO-LETTER INCOMPLETE

APPEARS THIS WAY

Endorsements:

R.Alivisatos/B.Leissa
S.Nerurkar
M.Anderson

DRAFTED MDA 9/29/96 X:\WPFILE\BIO\N74760D3.def

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

Date: 25-Sep-1996 01:55pm EDT
From: Cecelia Parise
PARISEC
Dept: HFD-615 MPN2 113
Tel No: 301-594-0315 FAX 301-594-0174

(ANDERSONM)

TO: Mark Anderson

Subject: FWD: ANDA 74-760

Mark,

Here is the information that HFD 520 needs to complete their review.

Cecelia

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

Date: 25-Sep-1996 01:40pm EDT
From: Brad Leissa
LEISSAB
Dept: HFD-520 CRP2 S337
Tel No: 301-827-2171 FAX 301-827-2325

TO: Cecelia Parise (PARISEC)

CC: Mary Fanning (FANNINGM)
CC: Regina Alivisatos (ALIVISATOSR)
CC: David Feigal (FEIGALD)
CC: Christina Chi (CHIC)

Subject: ANDA 74-760

Cecilia,

As we discussed over the telephone, Dr. Alivisatos had begun her review of ANDA 74-760 (Perrigo) and has found the following fundamental deficiencies in that she is *unable* to complete a review without the following rmation:

Absolute dates (versus relative dates) for ALL patient visits (e.g., pre-enrollment screening visit, enrollment visit, 1st posttherapy visit, and 2nd posttherapy visit).

Medication self-administration records for all patients. (e.g., 10/2/93-10/9/93)

Individual signs and symptoms values/scores for all patients at each visit.

In addition to the above *requirements*, please ask the applicant to calculate and report a mean clinical symptom score at each visit for both study arms for the applicant's evaluable population.

As we discussed, based on the magnitude of these deficiencies, you will probably generate a not approvable (NA) letter and send this to the applicant.

Thanks...Brad

GENERIC DRUGS ADVISORY COMMITTEE

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Summary Minutes of the Fourth Meeting
Ramada Inn, 8400 Wisconsin Avenue, Bethesda, Maryland
April 23-24, 1992

Committee Members Present

Terrence F. Blaschke, M.D.
Darrell Abernethy, M.D., Ph.D.
Gordon L. Amidon, Ph.D.
Barbara E. Hayes, Ph.D.
Kathleen R. Lamborn, Ph.D.
John H. Rodman, Pharm.D.
Leslie Z. Benet, Ph.D.
Judith I. Brown
Win L. Chiou, Ph.D.

Committee Member Absent

Kathleen M. Giacomini, Ph.D.

Partial list of FDA Participants and Attendees

Carl Peck, M.D.
Roger L. Williams, M.D.
Robert Jerussi, Ph.D.
P. K. Matura, Ph.D.
Jerome Skelly, Ph.D.
Charles Kumkumian, Ph.D.
Vinod Shah, Ph.D.
Gerald Meyer
John Treacy
Murray Lumpkin, M.D.
Paul Vogel
Michael Beatrice
Rashmikant Patel, Ph.D.
Agnes Wu, Ph.D.
Susan Alpert, M.D., Ph.D.

These summary minutes for the April 23-24, 1992 meeting of the Generic Drugs Advisory Committee were approved on December 1, 1992

"I certify that I attended the April 23-24, 2992 meeting of the Generic Drugs Advisory Committee and that these minutes accurately reflect what transpired."

/S/
Isaac F. Roubein, Ph.D.
Executive Secretary

/S/
Terrence F. Blaschke, M.D.
Chairman

12/27/95
(525)(j)(2)(A)
OK

PERRIGO COMPANY

REGULATORY AFFAIRS
616-673-7655 FAX

FACSIMILE TRANSMISSION

NDA ORIG AMEND
N/A

TO: MS. CECELIA PEREZ, CSO
OFFICE OF GENERIC DRUGS

COMPANY: FDA, CDER, OPS, OGD

DATE: DECEMBER 22, 1995

FROM: JACQUELINE EATON JAE
REGULATORY AFFAIRS MANAGER

TOTAL NUMBER OF PAGES: 26 including this page

IF THIS TRANSMISSION IS NOT SATISFACTORY, PLEASE CALL 616-673-7603

MESSAGE:

Please find attached Perrigo's Amendment to ANDA 74-760, Miconazole Nitrate Vaginal Cream 2%. The original signed document will be sent to FDA via overnight courier.

Thanks for the opportunity to discuss this issue with you earlier today.

Have a nice holiday.

APPEARS THIS WAY
ON ORIGINAL

Title I of Waxman-Hatch. Most of Title I had been finalized. They are now out from the Office of Management

2. Four days after the above Generic Drug Advisory Committee meeting, the ANDA Final Rules issued in the Federal Register Vol. 57, No. 62, Tuesday, April 28, 1992. FDA wrote in comment #44 of the ANDA Final Rules at page 17962 (attached):

". . . FDA has revised 314.94(a)(9) to require ANDA applicants to include such an [inactive ingredient] comparison only for drug products intended for parenteral use, ophthalmic or otic use, or topical use. ANDA applicants will be able to determine the inactive ingredients in reference listed drugs for these dosage forms because such ingredients are disclosed on the labeling . . ." (emphasis added).

Clearly, the intent of the ANDA Final Rules was for ANDA applicants to provide a qualitative comparison of the inactive ingredients for Miconazole Nitrate Vaginal Cream and not a quantitative comparison since the quantitative formula is not disclosed on Ortho's Monistat 7 Vaginal Cream product labeling. Perrigo provided a qualitative comparison of the inactive ingredients in the proposed ANDA 74-760. OTC manufacturer's do not have access to the innovator's quantitative formula because neither the FDA nor the innovator reveals this information.

Perrigo has a [redacted] October 30, 1992. Their product contains the same inactives as Perrigo's proposed drug product. Please see the quantitative and qualitative comparisons on Tables I and II, attached. [redacted], product is administered by the same route of administration as the reference listed drug. Perrigo obtained [redacted] formulation directly from [redacted] as provided for in the supply agreement. This agreement allows for (1) sourcing of finished product and (2) sharing of technical and formulation information on their approved ANDA product.

Additionally, Perrigo believed at the time of formulation and filing of the ANDA that the proposed drug product contained the same qualitative ingredients as the listed drug; i.e., that Glyceryl Monostearate plus [redacted] combined to form [redacted]. However, we believed that Glyceryl Monostearate needed to be included on the labeling. Perrigo is unclear as to why the listed drug does not indicate Glyceryl Monostearate on their labeling.

Perrigo also contends that information was already available to the Agency to determine that the inactive levels of the proposed drug were safe. That information is accessible to the Agency in the Inactive Ingredient Guide which list these inactives in the ranges for a drug of this route of administration. Also, the information in the clinical study for the proposed drug supports product safety. There were no unexpected adverse drug reactions reported. The stability profile also supports that these inactives do not adversely affect physical and chemical charateristics under stressed and real time storage.

(words of Dr. Roger Williams)

perhaps the methodology we talk about today could fail -- we will probably have to have recourse to a large-scale clinical trial.

The bias of the Office of Generic Drugs is that these large-scale clinical trials are not generally acceptable. They're cumbersome, they're expensive. I think they kind of defeat the purpose of Hatch Waxman. They're also insensitive. I think you can easily imagine that products that are inequivalent in a large clinical trial could still be labelled equivalent.

Anyway, if a generic applicant gets across these two main hurdles, the documentation of pharmaceutical equivalence and bioequivalence, then we can code them therapeutically equivalent, and they get that crucial AB rating in the orange book.

Just to give the committee a sense of where we are now in terms of topical products, for topical and vaginal antifungals, we did not have any blood level or pharmacologic effect methods available to document bioequivalence, so we are relying on clinical trials now for these particular products. We have no methodology in place for the topical anti-acne generic formulations, and we're going to be talking about the topical corticosteroids in this meeting.

The vasoconstrictor assay, as you all know from

(words of Dr. Murray Lumpkin)

that Dr. Williams put up previously. As he did say under the present situation, for a drug to be accepted as an ANDA, it has to come in in a vehicle that is similar, but there have been no regulations that have said that those vehicles have to be the same. Our experience has been that different cream vehicles that have been used with the same active ingredients have been quite different. Obviously, this brings up concerns.

I want to spend a couple of minutes talking about some concerns about safety as opposed to efficacy, because that is the general thing that we're talking about today, the efficacy. In the past, when we've had such variations in the various formulations for the vehicles, there have been questions that have been raised about potentials for sensitization, potentials for phototoxicity, potentials for irritants and potentials for allergenicity. But I think as Dr. Williams pointed out, under the new final rules for the Title I, we're at least now we know that the vehicles qualitatively are going to contain the same ingredients, even though quantitatively the quote-unquote inactive ingredients might be different. These concerns are somewhat more allayed than they have been in the past. So we can turn most of our attention to that of efficacy.

What we've been trying to do, and I think what you're going to spend most of the rest of your time today,

(Please see words of Dr. Murray Lumpkin)

DR. RODMAN: Just to be sure that I understood you correctly, you conclude that if there is pharmaceutical equivalence, given those criteria that you outline, that you accept safety.

DR. LUMPKIN: No, I think what this establishes is pharmaceutical therapeutic efficacy equivalence. It does not establish the safety of them. This was an issue that, prior to the final rules, was bandied about a great deal, because in the new drug application process, when a new product is coming in, we have very definitive set protocols that deal with the issue of sensitization, phototoxicity and allergenicity, that the innovator companies have to show that their formulation is not doing this type of thing, or if it is, there is a reasonable risk-benefit relationship to allow it to go forward.

But I think with the new final rules, at least having qualitatively the same ingredients in the formulations, it becomes less of a concern. All this is going to give us with the methodologies we talk about today. is a way that we can feel better about therapeutic equivalence, from an efficacy perspective, not from a safety perspective.

DR. HAYES: I'd just like to ask a question. Would you again describe your rationale for this validation proposal?

does not impose a pharmacokinetic data requirement for all labeling changes. In fact, FDA believes that most labeling changes that do not involve serious health or safety effects will be acceptable without new pharmacokinetic data. However, FDA also believes that some labeling changes may be formulation-specific and that such changes may require additional pharmacokinetic data (e.g., addition of a food effect statement). FDA, therefore, reserves the right to examine such labeling changes on a case-by-case basis to determine whether additional pharmacokinetic data are necessary before the ANDA holder changes labeling.

42. One comment proposed revising the third sentence in proposed § 314.194(a)(8)(iv), which listed certain permissible labeling differences between the ANDA drug product and the reference listed drug, to read as follows:

> Such differences protected by patent or accorded exclusivity by 505(j)(4)(D) of the act between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

The comment explained that the revision would protect ANDA applicants from "a possible claim of inducement or infringement where a nonapproved, but patented, method of administration is discussed in the innovator's label" or the labeling refers to more than one method of use and "some but fewer than all of the methods of use are entitled to nonpatent exclusivity."

FDA agrees in part with the comment and has amended the provision to state that differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include omissions of an indication "or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act."

Chemistry, Manufacturing, and Controls

FDA received a number of comments on the chemistry, manufacturing, and controls section of an ANDA.

43. Many comments sought further definitions or explanations regarding ANDA chemistry, manufacturing, and controls documentation requirements, including information on technical details, such as determining the source of impurities, potential degradation, and test methodologies. Two comments asked FDA to develop guidelines on acceptable levels of preservatives and other inactive ingredients.

These comments raise technical questions that are beyond the scope of this rule. FDA has already issued a number of guidelines addressing many of the questions. These guidelines apply to both full and abbreviated applications, and a list of available guidelines may be obtained from CDER Executive Secretariat Staff, Center for Drug Evaluation and Research (HFD–8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. FDA will consider the comments in determining whether to revise existing guidelines or to develop new guidelines.

44. Several comments objected to the provisions in proposed § 314.94(a)(9) requiring ANDA applicants to use the same inactive ingredients as the reference listed drug or to identify and characterize the differences between inactive ingredients. The comments stated that ANDA applicants might not know or might be unable to discover all inactive ingredients used in the reference listed drug. The comments suggested that FDA either not require that the inactive ingredients be the same or require the disclosure of the inactive ingredients used in the reference listed drug.

Because the labeling regulations do not require listing of inactive ingredients for drug products in an oral dosage form (see 21 CFR 201.100(b)(3)), ANDA applicants may be unable to discover what inactive ingredients were used in such drug products. Consequently, FDA has revised § 314.94(a)(9) to require ANDA applicants to include such a comparison only for drug products intended for parenteral use, ophthalmic or otic use, or topical use. ANDA applicants will be able to determine the inactive ingredients in reference listed drugs for these dosage forms because such ingredients are disclosed on the labeling. (See 21 CFR 201.100(b)(3).) For other drug products, FDA has revised § 314.94(a)(9)(ii) to require applicants only to identify and characterize the inactive ingredients in the proposed drug product and to provide information demonstrating that the inactive ingredients do not affect product safety.

45. Proposed § 314.94(a)(9)(iv) stated, in part, that:

> * * * an applicant may seek approval of a drug product (intended for ophthalmic or otic use) that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product, except that in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.
>
> (54 FR 28872 at 28923).

One comment objected to the example involving balanced salt solutions and isotonic saline solutions in proposed § 314.94(a)(9)(iv). The comment explained that changes in an ophthalmic buffer or tonicity agent from isotonic saline to balanced salt solutions do not raise serious safety questions, and FDA cannot presume that such changes are to claim a therapeutic advantage.

When read in its entirety, the second sentence in § 314.94(a)(9)(iv) simply states that an applicant whose product is intended for ophthalmic use cannot change a buffer or substance to adjust tonicity "for the purpose of claiming a therapeutic advantage over or difference from the listed drug * * *." The rule does not state that use of a balanced salt solution as opposed to an isotonic saline solution would be impermissible in itself or that FDA would presume such changes to be for claiming a therapeutic advantage. Determining whether the applicant claims a therapeutic advantage over or difference from the listed drug depends on the circumstances surrounding each case.

Samples

46. FDA received one comment regarding generic drug product samples under proposed § 314.94(a)(10). The proposed rule would require ANDA applicants to comply with the sampling provisions at 21 CFR 314.50 (e)(1) and (e)(2) but would not require ANDA applicants to submit samples until FDA requested them. The comment suggested revising the rule to require ANDA applicants to obtain samples and to retain them in their stability containers for all lots of a finished product. The comment added that FDA should "make itself available as a witness if requested for the distribution of samples to laboratories for bioavailability studies."

Under existing current good manufacturing practice (CGMP) regulations, manufacturers are already required to retain samples. (See 21 CFR 211.84 and 211.170.) FDA has also issued an interim rule that requires applicants who conduct in-house bioavailability and bioequivalence testing and contract laboratories who conduct such testing t

TABLE I

QUANTITATIVE COMPARISON OF THE PROPOSED DRUG PRODUCT WITH THE REFERENCE LISTED DRUG PRODUCT AND A PREVIOUSLY APPROVED DRUG PRODUCT ADMINISTERED BY THE SAME ROUTE OF ADMINISTRATION

Listed Drug NDA 17450	mg/g	Proposed Drug ANDA 74-760 Perrigo	mg/g
Miconazole Nitrate	20.0	Miconazole Nitrate	20.0
Benzoic Acid		Benzoic Acid	
BHA		BHA	
		Glyceryl Monostearate	
Mineral Oil		Mineral Oil	
Peglicol 5 Oleate		Peglicol 5 Oleate	
Pegoxol 7 Stearate		Pegoxol 7 Stearate	
Purified Water		Purified Water	

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

pages of trade secret and/or confidential commercial information

TABLE III

CONCENTRATION OF INACTIVE INGREDIENTS

FDA's Division of Drug Information Resources published an Inactive Ingredient Guide in October, 1993 showing the potency range for the following inactive ingredients presently in approved vaginal or topical cream drug products or conditionally approved vaginal or topical cream drug product currently marketed for human use. A copy of the appropriate pages are attached.

The potency in percent for each of Perrigo's inactive ingredients for the Miconazole Nitrate Vaginal Cream ANDA 74-760 are also indicated below.

In summary, the potency of each of Perrigo's inactive ingredients is equal to or within the potency published in the Inactive Ingredient Guide.

	Inactive Ingredient Guide Potency Range	Proposed Drug Product ANDA 74-760
Benzoic Acid	[redacted]	[redacted]
BHA		
Glyceryl Monostearate		
Mineral Oil		
Peglicol 5 Oleate		
Pegoxol 7 Stearate		
Purified Water		

APPEARS THIS WAY
ON ORIGINAL

Redacted 7

pages of trade secret and/or confidential commercial information

THE PERRIGO COMPANY
ANALYTICAL SERVICES
SPECIAL ASSAY REPORT

No. 10221

SAMPLE (S): MICONAZOLE NITRATE VAGINAL CREAM 2%

PRODUCT CODE: 214AA **LOT:** 4BH172

SOURCE: [redacted] **REQUESTED BY:** [redacted]

TESTED BY: [redacted] **REFERENCE:** AD159p2,3

COMMENTS

Analytical was requested by [redacted] to compare the physical characteristics of Perrigo's Miconazole Nitrate Vaginal Cream 2% to marketed products from two other manufacturers. The samples included Perrigo's test batch(PC#214AA, Lot#4BH172) and the reference batch(Monistat 7, Lot#24B904B) used in the bio-equivalency study.

TESTS	PERRIGO Lot#4BH172	COPLEY Lot#4SF873	Monistat 7 Lot#24B904B
WATER	[redacted]	[redacted]	[redacted]
SOLIDS	[redacted]	[redacted]	[redacted]
VISCOSITY	[redacted]	[redacted]	[redacted]
pH	[redacted]	[redacted]	[redacted]
SPECIFIC GRAVITY	[redacted]	[redacted]	[redacted]

APPEARS THIS WAY
ON ORIGINAL

PREPARED BY: /S/ **DATE:** 11/7/95 **CKD BY:** BVM

COPIES: [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-760

CORRESPONDENCE

PERRIGO®

April 15, 1997
VIA FEDERAL EXPRESS

Office of Generic Drugs, OPS, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Rashmikant M. Patel, Ph.D.
Director, Div. of Chemistry I

Telephone Amendment

AMENDMENT
N/Am

RE: Miconazole Nitrate Vaginal Cream, 2%
ANDA 74-760
Telephone Amendment

Dear Dr. Patel:

This letter is in response to the Agency's telephone communication on April 14, 1997, from Joe Buchinni. In this telephone communication, the Agency requested the L. Perrigo Company to clarify the raw material specification for Miconazole Nitrate USP, which had been previously submitted for ANDA 74-760, Miconazole Nitrate Vaginal Cream, 2% in the minor deficiency response dated August 9, 1996.

The raw material specification for Miconazole Nitrate, USP, has been revised to clarify the limits for the impurities and related substances and is enclosed. The improved specification references the same tests and limits as the previously submitted document, however, the testing descriptions are more consistent with the compendial references and with the manufacturer's certificate of analysis. In addition, a total related substances limit of — by — has been included.

Individual impurities and related substances are well controlled by the manufacturer in the drug substance at a level of less than — by both — and — assay methodologies. Total impurities are controlled to — by the USP Ordinary Impurities test using — and to — by the EP Related Substances test using —. In addition, the stability specifications for the finished drug product control impurities at a level of — individual and — total. The test results by the various assay methods (— systems) are not additive and provide separate control specifications.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company certifies that a "field copy", which is a true copy of this Telephone Amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

If you have any questions, please feel free to contact me by telephone at (616) 673-7604, by FAX at 616-673-7655 or by E-mail at GLUTKE@PERRIGO.COM.

Respectfully submitted,

Virginia G. Lutke

Virginia G. Lutke
Regulatory Affairs

RECEIVED
APR 16 1997
GENERIC DRUGS

enc.
xc: B. Schuster
G. Boerner

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

REGULATORY AFFAIRS DEPARTMENT
Fax: 616-673-7655

FACSIMILE TRANSMISSION

DATE: *April 15, 1997*

TO: *Mr. Joe Buchinni*
FAX # 1-301-594-0180

APPEARS THIS WAY
ON ORIGINAL

COMPANY: *FDA, Office of Generic Drugs*

FROM: *Ginger Lutke*

TEL. # *616-673-7604*

CC:

NUMBER OF PAGES (INCLUDING COVER PAGE) 6

MESSAGE:

RE: ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2% - Telephone Amendment

APPEARS THIS WAY
ON ORIGINAL

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

PERRIGO®

October 29, 1996
VIA FEDERAL EXPRESS

Office of Generic Drugs, OPS, 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

AMENDMENT

RE: Miconazole Nitrate Vaginal Cream, 2%
ANDA 74-760
Amendment

Dear Dr. Chan:

This letter is in response to the Agency's communication dated October 8,1996. In that letter, the Agency requested reformatted data for the bioequivalence study for ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2%.

Please see the attached responses to the Agency's comments. 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 by E-mail at GGREEN@PERRIGO.COM.

Respectfully submitted,

Virginia K. Green

Virginia K. Green
Regulatory Affairs

xc: J. Eaton
D. Jespersen

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

ANDA 74-760

L. Perrigo Company
Attention: Jacqueline Eaton
117 Waters Street
Allegan MI 49010

MAR 18 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Miconazole Nitrate Vaginal Cream, 2%.

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

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

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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NDA CRIC AMENDMENT

N/A F

October 16, 1996

Office of Generic Drugs, CDER, OPS, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Jerry Phillips
Director, Div. of Labeling and Program Support

Telephone Amendment

Review completed 12/17/96

RE: ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2%
Final Printed Labeling for Packaging Inserts

Dear Mr. Phillips:

Per the Office of Generic Drugs request by Lilly Golson on Friday, September 20, 1996, enclosed is final printed labeling for the package inserts for ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2% - Reusable Applicator and Disposable Applicators.

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

Best regards,

Virginia K. Green

Virginia K. Green
Sr. Regulatory Affairs Admin.

xc: J. Eaton
D. Jespersen

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October 4, 1996

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

RE: ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2%
Confirmation Copy of Fax

Dear Dr. Visatos:

For ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2%, enclosed is a hard copy of the facsimile which was sent to you today.

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

Best regards,

Virginia K Green

Virginia K. Green
Sr. Regulatory Affairs Admin.

xc: J. Eaton
D. Jespersen
C. Parise (Office of Generic Drugs)

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October 1, 1996

NEW CORRESP

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GENERIC DRUGS

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

RE: ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2%
Telephone Conversation

Dear Dr. Visatos:

Per our conversation today concerning the "Days" column in the reformatted data tables which were submitted to the Agency on March 20, 1996, please see the attached letter from [redacted]. The "Days" column indicates the number of days after the completion of the 7 day treatment period. It **does not** indicate the study day number where treatment would be considered study days 1-7 and the first follow-up would be due on study day 14.

Please note that there were a number of minor protocol violations which were explained in the 03/20/96 amendment. It is our opinion that these minor protocol violations did not affect the outcome of the study. If you are of the opinion that any of these minor protocol violations should not be included in the study, please contact me immediately by telephone so we may promptly address any issues with these patients you may have. An explanation of the minor protocol violations is also enclosed with this letter.

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

Best regards,

Virginia K. Green

Virginia K. Green
Sr. Regulatory Affairs Admin.

xc: J. Eaton
D. Jespersen
C. Parise (Office of Generic Drugs)

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

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NDA ORIG AMENDMENT

RECEIVED

AUG 12 1996

GENERIC DRUGS

August 9, 1996
VIA FEDERAL EXPRESS

Office of Generic Drugs, OPS, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Rashmikant M. Patel, Ph.D.
Director, Div. of Chemistry I

MINOR AMENDMENT

RE: Miconazole Nitrate Vaginal Cream, 2%
ANDA 74-760
Minor Amendment

Dear Dr. Patel:

This letter is in response to the Agency's communication dated July 2, 1996. In that letter, the Agency commented on the L. Perrigo Company's ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2% dated September 29, 1995. This application was also amended December 22, 1995 and January 31, 1996.

In a letter to the Agency dated July 18, 1996, the L. Perrigo Company stated they would respond to the Agency's comments within 30 days. The L. Perrigo Company is now amending this application and responding to the Agency's comments in the July 2, 1996 correspondence.

Please see the attached responses to the Agency's comments. 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 by E-mail at GGREEN@PERRIGO.COM.

Respectfully submitted,

Virginia K Green

Virginia K. Green
Regulatory Affairs

xc: J. Eaton
D. Jespersen
E. Pileggi

8.16.96

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

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CONFIRMATION COPY
mailed per
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)

RECEIVED
MAR 29 1996
GENERIC DRUGS

Melissa 3/29/96

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

PERRIGO®

|S| 7/29/96

RECEIVED

JUL 19 1996

GENERIC DRUGS

July 18, 1996
VIA FEDERAL EXPRESS

Office of Generic Drugs, OPS, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Rashmikant M. Patel, Ph.D.
Director, Div. of Chemistry I

MINOR DEFICIENCY RESPONSE

NEW CORRESP
NC

RE: Miconazole Nitrate Vaginal Cream, 2%
ANDA 74-760
Minor Deficiency Response

Dear Dr. Patel:

This letter is in response to the Agency's communication dated July 2, 1996. In that letter, the Agency commented on the L. Perrigo Company's ANDA 74-760 Miconazole Nitrate Vaginal Cream, 2% dated September 29, 1995. This application was also amended December 22, 1995 and January 31, 1996.

The L. Perrigo Company will respond to all comments listed in the Agency's 7/2/96 communication within 30 days. If you have any questions, please feel free to contact me by telephone at (616) 673-7604, by FAX at 616-673-7655 or by E-mail at GGREEN@PERRIGO.COM.

Respectfully submitted,

Virginia K. Green

Virginia K. Green
Regulatory Affairs

xc: J. Eaton
D. Jespersen
E. Pileggi

|S| 7-25-96

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

PERRIGO®

Orig

mail yr
BIOAVAILABILITY

March 20, 1996

ORIG NEW CORRES

RECEIVED

MAR 21 1996

GENERIC DRUGS

Office of Generic Drugs, 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 Cream
ANDA 74-760

Dear Dr. Piver:

This letter is in response to your faxed communication to the Perrigo Company on February 16, 1996. In that letter, you requested certain parts of the bioequivalence data for ANDA 74-760 Miconazole Nitrate Vaginal Cream be reformatted to conform to the Agency's protocol for reviewing ANDA's.

The clinical research organization which performed the study, _____, has reformatted the data as requested. Please see the enclosed information.

In regards to the clarification of number of patient visits, the protocol required 4 visits as follows:

Visit 1: Patient Screening (medical history, physical exam, gynecological examination, vaginal secretion collection for culture, sign and symptom assessment, urine pregnancy test).
Visit 2: Baseline Assessments (blood and urinalysis and drug distribution).
Visit 3: First follow up visit 7-10 days post-treatment including gynecological examination, vaginal secretion collection for culture, and sign and symptom assessment.
Visit 4: Second follow up visit 28-34 days post-treatment including gynecological examination, vaginal secretion collection for culture, and sign and symptom assessment.

Also, please note for 3 tables, "All Eligible Enrolled Patients (baseline data)", "All Ineligible Enrolled Patients (baseline data)" and "Visit Specific Clinical Cure Rates", the signs (physicians assessment only) have been given rather than a combination of signs and symptoms (physician and patient assessments) per your direction in a telephone conversation with me (Ginger Green) on March 5, 1996.

/s/ 7-25-96

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

If you have any questions or need any additional information, please feel free to contact me by telephone at (616) 673-7604 or by FAX at 616-673-7655.

Thank-you for your prompt review of this application.

Respectfully submitted,

Virginia K. Green

Virginia K. Green
Regulatory Affairs

cc: J. Eaton

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-760

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

JUL 2 1996

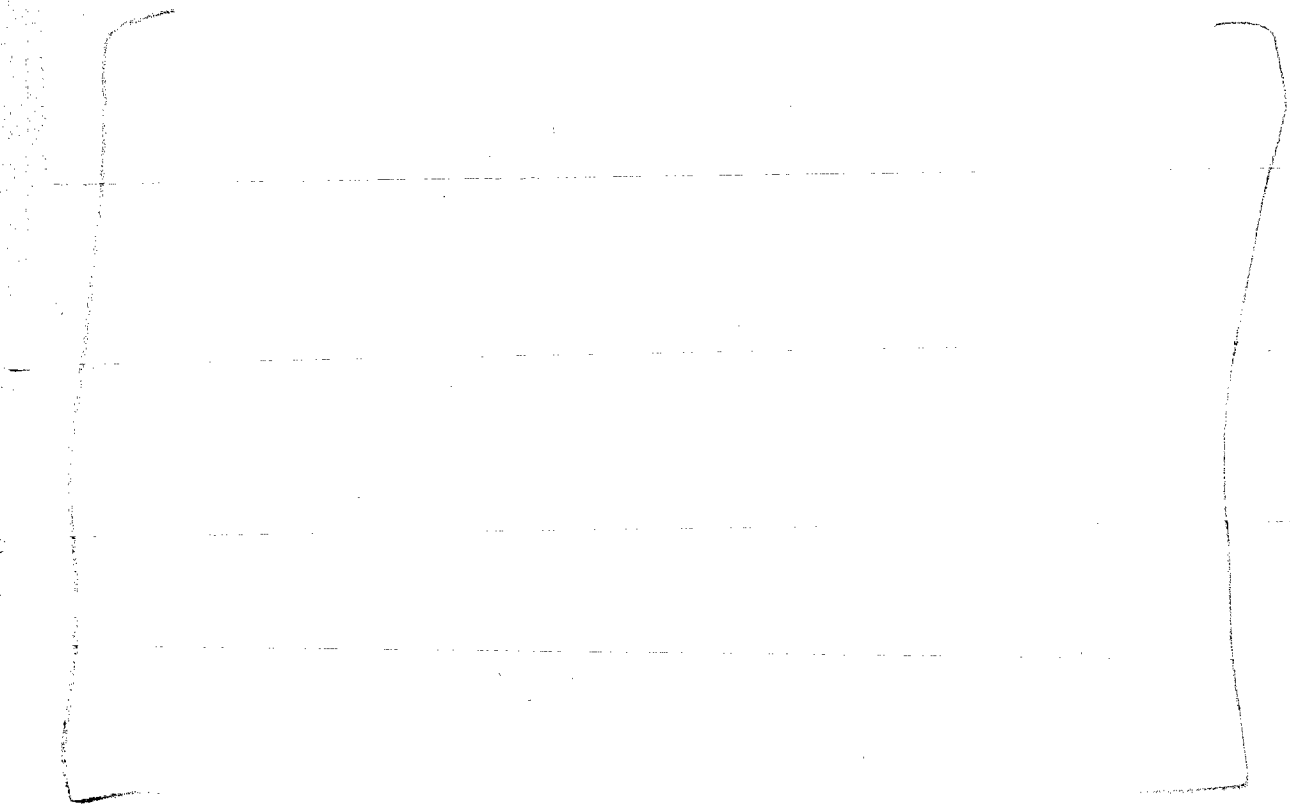
Dear Madam:

This is in reference to your abbreviated new drug application dated September 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Cream, 2%.

Reference is also made to your amendments dated December 22, 1995, and January 31, 1996.

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

A. Chemistry Deficiencies



6. You claim on page 9 that there is no market exclusivity for the listed drug product Monistat 7 combination pack. That is not the correct listed drug for this ANDA. Please correct.

B. Labeling Deficiencies

1. CONTAINER (45 g tube)

   Revise your expression of strength to read, "Miconazole Nitrate Vaginal Cream, 2%".

2. CARTON (1 reusable applicator)
   (7 disposable applicators)

   See CONTAINER comment.

3. EDUCATIONAL BROCHURE

   a. See CONTAINER comment.

   b. Directions for Use

      Revise to include the following step and accompanying drawing:

      After each use, replace cap and roll tube from bottom (as shown).

      (Please note: Neither the text nor the drawing are included in your December 22, 1995 submission; however, the drawing but not the text is included in your January 31, 1996 submission.)

Revise your package insert labeling, as instructed above, and submit the container labels, carton and insert labeling in final print. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

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

B. Your bio study is under review.

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

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 7/11/96

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

cc: ANDA #74-760
ANDA #74-760/DUP/Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-627/N.Nashed/5-14-96 6/18/96
HFD-613/L.Golson/6-10-96 /S/ 6/27/96
HFD-613/A.Vezza for J.Phillips/6-11-96 /S/ for W 6/28/96
HFD-627/P.Schwartz, Ph.D./5-15-96 /S/ 6/18/96
HFD-617/B.Russell, CSO/6-11-96 /S/ 6/28/96
X:\WPFILE\MAJORS\NASHED\74-760.LI
F/T by MM June 17, 1996
Not Approvable - Major

February 8, 1996

Ms. Jacqueline M. Eaton
Regulatory Affairs Manager
Perrigo Company
117 Water Street
Allegan, Michigan 49010

RE: ANDA 74-760

Dear Ms. Eaton:

I am in the process of conducting my review of the above ANDA. The data do not include several items necessary for my evaluation. As we did in ANDA 74-395, I am requesting reformatting of some of the 74-760 material to conform to our protocol for reviewing ANDAs. Your prompt attention to this request will greatly assist me in conducting and facilitating my review of this ANDA in an expeditious and consistent manner.

Thank you for your assistance.

Very truly yours,

/S/

Julius S. Piver, M.D.
Medical Officer
FDA/CDER/HFD-520

9201 Corporate Boulevard
Room N-332
Gaithersburg, Maryland 20857

301 827-2181 - Phone
301 827-2327 - Fax

CC: Cecelia Parise, Office Generic Drugs
Janice Soreth,M.D., SMO

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

January 31, 1996

Dr. Charles Ganley
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **Miconazole Cream Amendment for Disposable Applicators ANDA 74-760**

AMENDMENT ANDA 74-760

Dear Dr. Ganley:

Please find enclosed Perrigo's Amendment to ANDA 74-760, Miconazole Nitrate Vaginal Cream 2%. This Amendment is being filed under 21 CFR 314.60.

The purpose of the Amendment upon FDA approval, is to allow Perrigo the option of marketing the proposed drug product with seven disposable two-piece applicators and associated labeling. The [redacted] of the disposable applicators is [redacted]. whose [redacted]

Perrigo's ANDA 74-760 accepted for filing on December 22, 1995 includes packaging and labeling information for a re-usable applicator. Upon approval of the ANDA, including this amendment, Perrigo could market product under two packaging options: (1) the re-usable applicator and associated labeling and (2) the disposable applicators and associated labeling.

An index of items included in this Amendment follows.

Respectfully submitted,

Jacqueline M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

xc: D. Jespersen, B. Pileggi, N. Wilmore

117 WATER STREET • ALLEGAN, MICHIGAN 49010 • (616) 673-8451

AND 74-760

L. Perrigo Company
Attention: Elizabeth M Pileggi
117 Water Street
Allegan, MI 49010

DEC 28 1995

Dear Madam:

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

Reference is also made to our "Refuse to File" letter dated October 19, 1995, and your amendment dated December 22, 1995.

NAME OF DRUG: Miconazole Nitrate Vaginal Cream, 2%

DATE OF APPLICATION: September 29, 1995

DATE OF RECEIPT: October 2, 1995

DATE ACCEPTABLE FOR FILING: December 22, 1995

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 AND number shown above.

Should you have questions concerning this application, contact:

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

/S/ 12/28/95

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

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

December 22, 1995
VIA FEDERAL EXPRESS

Dr. Charles Ganley, M.D., Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT
ANDA 74-760

RE: Miconazole Nitrate Vaginal Cream, 2%
ANDA 74-760

Dear Dr. Ganley:

Perrigo is filing this amendment to ANDA 74-760 in response to the Agency's letter dated October 19, 1995 for Miconazole Nitrate Vaginal Cream, 2%. The Agency's questions and Perrigo's response to those questions were reviewed with William Russell, Consumer Safety Officer at FDA, on October 24, 1995.

Perrigo contends that the regulations do not require a comparison demonstrating that the proposed drug product is **quantitatively** the same as the reference listed drug product. Perrigo believes the agency has erroneously and unfairly applied the regulations in issuing the refusal to file letter. Therefore, the file date for Perrigo's Miconazole Nitrate Vaginal Cream ANDA 74-760 is respectfully requested to be on or about September 29, 1995.

The following information supports Perrigo's position:

1. In an effort to understand more about FDA's views on topical products, Perrigo attended FDA's Generic Drug Advisory Committee meeting on April 24, 1992 wherein Drs. Roger Williams and Murray Lumpkin stated that inactive ingredients for topical products do not need to be present in the same proportions as the innovator product. Please see attached pages 264, 265, 281 and 287 from the certified transcript of the meeting.

2. Four days after the above Generic Drug Advisory Committee meeting, the ANDA Final Rules issued in the Federal Register Vol. 57, No. 62, Tuesday, April 28, 1992. FDA wrote in comment #44 of the ANDA Final Rules at page 17962 (attached):

". . . FDA has revised 314.94(a)(9) to require ANDA applicants to include such an [inactive ingredient] comparison only for drug products intended for parenteral use, ophthalmic or otic use, or topical use. ANDA applicants will be able to determine the inactive ingredients in reference listed drugs for these dosage forms because such ingredients are disclosed on the labeling . . ." (emphasis added).

Clearly, the intent of the ANDA Final Rules was for ANDA applicants to provide a qualitative comparison of the inactive ingredients for Miconazole Nitrate Vaginal Cream and not a quantitative comparison since the quantitative formula is not disclosed on Ortho's Monistat 7 Vaginal Cream product labeling. Perrigo provided a qualitative comparison of the inactive ingredients in the proposed ANDA 74-760. OTC manufacturer's do not have access to the innovator's quantitative formula because neither the FDA nor the innovator reveals this information.

Perrigo has a contractual supply agreement with [redacted] on October 30, 1992. Their product contains the same inactives as Perrigo's proposed drug product. Please see the quantitative and qualitative comparisons on Tables I and II, attached. [redacted] product is administered by the same route of administration as the reference listed drug. Perrigo obtained [redacted] formulation directly from [redacted] as provided for in the supply agreement. This agreement allows for (1) sourcing of finished product and (2) sharing of technical and formulation information on their approved ANDA product.

Additionally, Perrigo believed at the time of formulation and filing of the ANDA that the proposed drug product contained the same qualitative ingredients as the listed drug; i.e., that Glyceryl Monostearate plus [redacted] combined to form [redacted] However, we believed that Glyceryl Monostearate needed to be included on the labeling. Perrigo is unclear as to why the listed drug does not indicate Glyceryl Monostearate on their labeling.

Perrigo also contends that information was already available to the Agency to determine that the inactive levels of the proposed drug were safe. That information is accessible to the Agency in the Inactive Ingredient Guide which list these inactives in the ranges for a drug of this route of administration. Also, the information in the clinical study for the proposed drug supports product safety. There were no unexpected adverse drug reactions reported. The stability profile also supports that these inactives do not adversely affect physical and chemical charateristics under stressed and real time storage.

In an effort to provide the Agency with the information requested, Perrigo was able to determine the quantitative formula of the listed drug with the exception of Peglicol 5 oleate and mineral oil. These excipients were unable to be quantified even after using [redacted] and several other analytical methods of analysis.

The safety information requested in the Agency's October 19, 1995 letter is outlined below:

(A) The inactive ingredients in the proposed drug product have been previously approved by FDA in [redacted] The [redacted] product is administered by the same route of administration as Perrigo's proposed drug product.

(B) Please find attached Table III demonstrating that the concentrations of the inactive ingredients of the proposed drug product are within the concentration ranges previously approved for drug products administered by the same route of administration. The FDA Inactive Ingredient Guide (applicable pages are attached), in FDA's possession, displays the potency ranges for inactive ingredients in approved or conditionally approved drug products marketed for human use.

(C) A comparison of the physical and chemical properties of the proposed drug product with those of the reference listed drug product as well as [redacted], are attached in the Special Assay Report No. 10221.

(D) Perrigo's stability data and bioclinical information included in ANDA 74-760 show that the inactive ingredients do not adversely affect the physical and chemical properties of the drug product. Further, the bioclinical information and lack of unexpected adverse drug reactions, support the safety of the inactives in the proposed drug which is administered through the same route as the listed drug.

In conclusion, the regulations do not require a comparison demonstrating that the proposed drug product is quantitatively the same as the reference listed drug product. In addition, Perrigo provided information in the ANDA which demonstrates that the qualitative difference between our drug product and the reference listed drug do not affect the safety of the proposed drug product. Perrigo believes it is inappropriate and unfair for FDA to require the information requested in the Agency's correspondence of October 19, 1995. To obtain such information creates an economic disadvantage for generic firms in that it is costly to determine the complete quantitative formulation of the listed drug's proprietary formula, and is sometimes scientifically unfeasible.

Since the Agency had all appropriate information available to them to determine fileability of the application, Perrigo respectfully requests that the file date for ANDA 74-760 be recognized as on or about September 29, 1995.

In addition, please find enclosed original signatures for the cover letter and a third field copy certification as requested in your correspondence of October 19, 1995.

If you have any further questions, please contact me directly at 616-673-7670 or at the address on this letterhead.

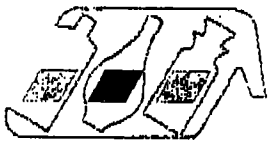
Respectfully submitted,

David A. Jespersen
Director, Technical Services

Jacqueline M. Eaton
Regulatory Affairs Manager

cc: B. Pileggi, D. Jespersen, G. Jazdzyk

APPEARS THIS WAY
ON ORIGINAL



PERRIGO COMPANY

FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

September 29, 1995

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

Re: Miconazole Nitrate Vaginal Cream 2%
Abbreviated New Drug Application

Dear Dr. Ganley:

The L. Perrigo company is submitting for your review and approval, an ANDA for Miconazole Nitrate Vaginal Cream 2%. This ANDA is being filed pursuant to 505(j) of the Federal Food, Drug, Cosmetic Act. Perrigo's product is identical in strength, indications, active ingredient, route of administration and dosage form to RW Johnson's MONISTAT® 7 miconazole nitrate vaginal cream.

MONISTAT® 7 vaginal cream (N17450 002) is listed in the Fifteenth Edition of Approved Drug Products with Therapeutic Equivalence Evaluations as an OTC drug with no patent protection or market exclusivity.

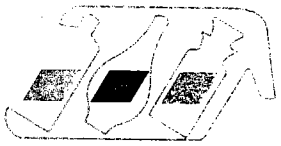
Should you require additional information, please contact me directly at 616-673-7670 or the address on this letterhead.

Respectfully submitted,

J. M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

ORIGINAL



PERRIGO COMPANY

FROM LAB TO LABEL - QUALITY HEALTH AND BEAUTY PRODUCTS

November 1, 1995

REQUEST FOR INFORMAL CONFERENCE

Mr. Jerry Phillips
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG NEW CORRES

Re: **Miconazole Nitrate Vaginal Cream, 2%**
ANDA 74-760

Dear Mr. Phillips:

Perrigo is requesting an informal conference with the Agency to discuss the correspondence dated October 19, 1995 in reference to ANDA 74-760 for Perrigo's Miconazole Nitrate Vaginal Cream wherein the Agency refused the application for filing.

Perrigo initially contacted William Russell, Consumer Safety Officer to discuss the issue presented in the October 19 correspondence. However, Perrigo is looking for further guidance from FDA on this issue; specifically the requirement for a quantitative comparison of inactive ingredients as well as how the information can practically be obtained.

The persons at Perrigo who plan to attend the informal conference are:

Jacqueline Eaton, Regulatory Affairs Manager
Greg Jazdzyk, Director of Liquid Research & Development
David Jespersen, Director of Technical Services
Bill VanMeter, Chief Chemist

Please call me at 616-673-7670 if you have any questions or require further information.

Respectfully submitted,

Jacqueline M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

RECEIVED
NOV 0 2 1995
GENERIC DRUGS

117 WATER STREET • ALLEGAN, MICHIGAN 49010 • (616) 673-8451

1 copy only

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 Miconazole Nitrate 2% Vaginal Cream Abbreviated New Drug Application 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
Food & Drug Administration
1560 Jefferson Ave.
Detroit, MI 48207

Jacqueline M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

1.1
N. Nash 2

ANDA 74-760

OCT - 8 1996

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

Dear Madam:

Reference is made to the Abbreviated New Drug Application, submitted on September 29, 1995, for Miconazole Nitrate Vaginal Cream.

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 following additional information is required before HFD-520 is able to complete a substantive review of the data submitted:

1. Please submit summary information in line form by center for each patient, in include demographics, date of enrollment, dates of therapy, dates of post-therapy visits and their relationship to the treatment stop date.

2. Please provide information describing when each patient self-administered the drug.

3. Please provide individual signs and symptoms values/scores for all patients at each visit.

4. Please calculate and report a mean clinical symptom score at each visit for both study arms for the evaluable population.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter.

Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-760

L. Perrigo Company
Attention: Elizabeth M. Pileggi
117 Water Street
Allegan, MI 49010

OCT 19 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated September 29, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Miconazole Nitrate Vaginal Cream, 2%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

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

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

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

In addition, while we note that you have provided the required certifications with your application, you have failed to insure that all those documents that require original signatures in the Archival copy have been signed. Please be aware that original signatures, when required, should be provided in the **archival** copy of the application. Please provide, with original signatures, a cover letter and a third (field) copy certification.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 10/19/95

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

ANDA 74-760
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Act- ief /S/ 10/18/95 date
HFD-615/WRussell, CS /S/ 10/13/95 date
HFD-610/CHoppes, Act. Chief, LR /S/ 10/19/95 date
HFD-629/PSchwartz, Sup. Chem. /S/ 10/19/95 date
WP File\russell\74\74-760
F/T by Fox 10/13/95
ANDA Refuse to File!

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

L PERRIGO
117 WATER ST
ALLEGAN MI 49010

ANDA #: N074760

Dear Sir/Madam:

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

NAME OF DRUG:
MICONAZOLE NITRATE Vaginal Cream,
Dosage Form: ~~CRM~~ Potency: 2% ~~VAGINAL~~ USP:

DATE OF APPLICATION: 29-SEP-95

DATE OF RECEIPT: 02-OCT-95

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

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

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

Sincerely yours,

/S/

Schwartz
Rodosevich
HFD-629

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

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

Refer to file 10/12/95

September 29, 1995

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

Re: **Miconazole Nitrate Vaginal Cream 2%**
Abbreviated New Drug Application

Dear Dr. Ganley:

The L. Perrigo company is submitting for your review and approval, an ANDA for Miconazole Nitrate Vaginal Cream 2%. This ANDA is being filed pursuant to 505(j) of the Federal Food, Drug, Cosmetic Act. Perrigo's product is identical in strength, indications, active ingredient, route of administration and dosage form to RW Johnson's MONISTAT^R 7 miconazole nitrate vaginal cream.

MONISTAT^R 7 vaginal cream (N17450 002) is listed in the Fifteenth Edition of Approved Drug Products with Therapeutic Equivalence Evaluations as an OTC drug with no patent protection or market exclusivity.

Should you require additional information, please contact me directly at 616-673-7670 or the address on this letterhead.

Respectfully submitted,

Jacqueline M. Eaton

Jacqueline M. Eaton
Regulatory Affairs Manager

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