CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-915

Generic Name: Tioconazole Vaginal Ointment, 6.5%

Sponsor: L. Perrigo Company

Approval Date: November 21, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-915

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-915

APPROVAL LETTER

ANDA 75-915

NOV 21 2001

L. Perrigo Company
Attention: Brian R. Schuster
515 Eastern Ave.
Allegan, MI 49010

Dear Sir:

This is in reference to your abbreviated new drug application dated June 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Tioconazole Vaginal Ointment, 6.5% (OTC).

Reference is also made to your amendments dated October 12, 2000; February 1, March 5, May 15, May 29, August 14, September 13, October 2, and October 11, 2001.

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 Tioconazole Vaginal Ointment, 6.5%, to be bioequivalent to the listed drug (Vagistat®-1 Vaginal Ointment, 6.5%, of Bristol Myers Squibb Co).

Under Section 506A of the Act, 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 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

/S/

Gary Buehler 11/21/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

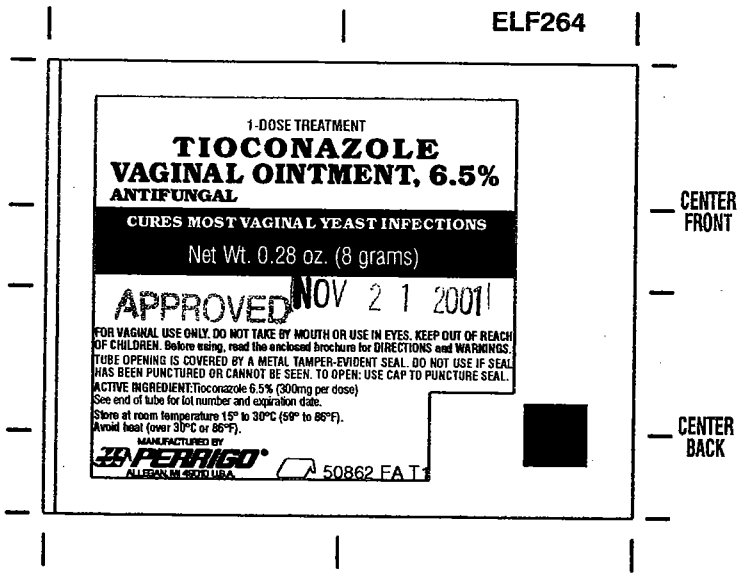
75-915

Final Printed Labeling

75-915

AP 11/21/01

Final Printed Labeling
ANDA 75-915
Tioconazole Vaginal Ointment, 6.5%
Tube



Drug Facts

Active ingredient (in each applicator) — **Purpose**

Tioconazole 300 mg (6.5%) — Vaginal antifungal

Use

■ treats vaginal yeast infections

Warnings

For vaginal use only

Do not use

■ if you have never had a vaginal yeast infection diagnosed by a doctor
■ if you have a fever (higher than 100°F), pain in the lower abdomen, back, or either shoulder, or foul-smelling vaginal discharge. You should see a doctor for these symptoms.

Ask a doctor before use if you have

■ vaginal itching and discomfort for the first time
■ symptoms that return within 2 months. You could be pregnant or have a serious underlying medical cause for your symptoms including diabetes or a weakened immune system (which may be due to HIV - the virus that causes AIDS).

When using this product

■ do not use tampons, douches, spermicides, or other vaginal products
■ do not use condoms or diaphragms as this product may damage them and they may not prevent sexually transmitted disease or pregnancy
■ do not have vaginal intercourse
■ wait 3 days after treatment to resume using condoms or a diaphragm

1-DOSE TREATMENT

TIOCONAZOLE OINTMENT 6.5%

VAGINAL ANTIFUNGAL

CURES MOST VAGINAL YEAST INFECTIONS

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

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PERRIGO®
ALLEGAN, MI 49010 U.S.A.

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CODE AREA

1-DOSE TREATMENT

TIOCONAZOLE OINTMENT 6.5%

VAGINAL ANTIFUNGAL

CURES MOST VAGINAL YEAST INFECTIONS

1 Disposable Applicator

Educational Brochure Enclosed

Net Wt. 0.28 oz. (8 grams)

Drug Facts (continued)

Inactive ingredients butylated hydroxyanisole, magnesium aluminum silicate, white petrolatum

Questions? If you have questions of a medical nature, please contact your pharmacist, doctor, or health care professional.

1-DOSE TREATMENT

TIOCONAZOLE OINTMENT 6.5%

VAGINAL ANTIFUNGAL

CURES MOST VAGINAL YEAST INFECTIONS

Drug Facts (continued)

Other information

■ this product is a 1-dose treatment; most women do not experience complete relief of their symptoms in just one day. Most women experience some improvement within 1 day and complete relief of symptoms within 7 days.
■ if you have questions about vaginal yeast infections, consult your doctor
■ store at 15° to 30°C (59° to 86°F)
■ see end panel and tube for lot number and expiration date

Final Printed Labeling
ANDA 75-915
Tioconazole Ointment 6.5%
Vaginal Antifungal

APPROVED NOV 2 1 2001

EFB136

15

Drug Facts

Active ingredient (in each applicator)
Tioconazole 300 mg (6.5%) ..... **Purpose** Vaginal antifungal

Use
- treats vaginal yeast infections

Warnings
For vaginal use only

Do not use
- if you have never had a vaginal yeast infection diagnosed by a doctor
- if you have a fever (higher than 100°F), pain in the lower abdomen, back, or either shoulder, or foul-smelling vaginal discharge. You should see a doctor for these symptoms.

Ask a doctor before use if you have
- vaginal itching and discomfort for the first time
- symptoms that return within 2 months. You could be pregnant or have a serious underlying medical cause for your symptoms including diabetes or a weakened immune system (which may be due to HIV - the virus that causes AIDS).

When using this product
- do not use tampons, douches, spermicides, or other vaginal products
- do not use condoms or diaphragms as this product may damage them and they may not prevent sexually transmitted disease or pregnancy
- do not have vaginal intercourse
- wait 3 days after treatment to resume using condoms or a diaphragm

Stop use and ask a doctor if
- symptoms do not get better after 3 days
- symptoms last for more than 7 days. You may have a condition other than a yeast infection
- you get a rash, fever, abdominal pain, or a foul-smelling vaginal discharge

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- before using, read the enclosed brochure for complete instructions and information.
- adults and children 12 years and over: open the tube just before use. Fill the applicator and insert entire contents of applicator into the vagina, preferably at bedtime.
- children under 12: ask a doctor

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75-915

1-DOSE TREATMENT

TIOCONAZOLE OINTMENT 6.5%
VAGINAL ANTIFUNGAL

CURES MOST VAGINAL YEAST INFECTIONS

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

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1-DOSE TREATMENT

TIOCONAZOLE

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1-DOSE TREATMENT

TIOCONAZOLE VAGINAL OINTMENT, 6.5%

ANTIFUNGAL

5 WHEN CAN YOU EXPECT SYMPTOM RELIEF?

While this product is a 1-dose treatment, most women do not experience complete relief of their symptoms in just one day. Most women experience some improvement within 1 day and complete relief of symptoms within 7 days.

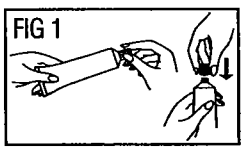
If your symptoms do not improve in 3 days or if you still have symptoms after 7 days, consult your doctor. Your doctor may recommend other treatment, or you may have a condition other than a yeast infection.

If your symptoms return within 2 months or if you think you have been exposed to the human immunodeficiency virus (HIV) that causes AIDS, consult your doctor immediately. Recurring yeast infections may be a sign of pregnancy or a serious condition, such as AIDS or diabetes.

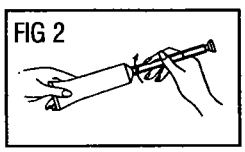
6 HOW TO USE TIOCONAZOLE VAGINAL OINTMENT, 6.5%

Directions for use:

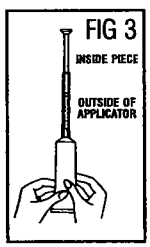
- **Read the full directions printed below carefully before using.**
- Bedtime is the best time to apply this product.
- To open the tube, unscrew the cap. Turn the cap upside down and place the cap in the end of the tube. Push down firmly until the seal is broken. FIG 1



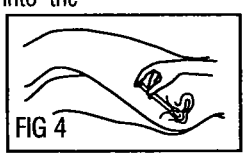
- Attach the applicator to the tube by turning applicator clockwise. FIG 2



- Squeeze the tube from the bottom. This will force the ointment 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. FIG 3



- Lie on your back with your knees bent. Gently insert applicator into the vagina as far as it will go comfortably. Push the plunger into the applicator until it will go no further. FIG 4
- Withdraw the applicator and plunger and dispose of it in the wastebasket. Do not flush.



- DO NOT USE TAMPONS while using this medicine. Use sanitary napkins instead.

7 ADVERSE REACTIONS (SIDE EFFECTS)

A temporary increase in vaginal burning, itching and/or irritation may be experienced upon insertion of this ointment. These reactions, in addition to vaginal swelling or redness; difficulty in burning on urination; headache; abdominal pain/cramping and upper respiratory infection have been reported with the use of this product. If you experience any of these, consult your doctor.

8 COMMON QUESTIONS ABOUT VAGINAL YEAST INFECTIONS AND TIOCONAZOLE VAGINAL OINTMENT, 6.5%

Q. Should I use this product while I have my period?

You can use this product while menstruating but you should not use tampons following application. Use sanitary napkins instead.

Q. Can I have sex while using this product?

It is generally recommended not to have vaginal intercourse the first few nights after treatment with this product.

Q. Can I use a condom or diaphragm while using this product?

No. This product contains petrolatum which may damage the latex from which condoms and diaphragms are made and may cause them to fail. This may reduce their effectiveness in preventing sexually transmitted diseases and pregnancy. You should wait 3 days after treatment to resume using condoms or your diaphragm.

Q. Does my partner need to be treated?

Yeast infections occur less frequently in men than in women. However, if your partner has any of the following symptoms: itching, redness or discomfort in the genital area, he should see a doctor and mention that you are treating a vaginal yeast infection.

Q. Can I use feminine hygiene products (such as douche) while I have a vaginal yeast infection?

It is best not to use any vaginal preparations while you have a yeast infection including douches, feminine hygiene sprays, contraceptive foams, inserts, or jellies.

9 FOR BEST RESULTS

- **Wear cotton underwear and loose-fitting clothes -** Yeast grow in warm, moist environments. Wearing loose-fitting cotton clothes helps create a cooler environment, which makes it more difficult for yeast to grow.
- **Change out of wet bathing suit quickly -** Dampness is more likely to encourage the growth of yeast.
- **Use proper hygiene -** Wipe from front to rear (away from vagina) after a bowel movement or urination.
- **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 any questions or concerns about vaginal yeast infections or of a medical nature, don't hesitate to consult your doctor.

CONTENTS

Active ingredient: Tioconazole 6.5% (300mg per dose).

Inactive ingredients: Butylated hydroxyanisole, magnesium aluminum silicate and white petrolatum.

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

Do not use if sealed tube is broken, or incompletely sealed. For expiration date and lot number, see carton end flap and end of tube.

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1-DOSE TREATMENT
TIOCONAZOLE VAGINAL OINTMENT, 6.5%
ANTIFUNGAL
EDUCATIONAL BROCHURE

Please read this educational brochure completely before using this product.

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

1 THIS PRODUCT CURES MOST RECURRENT VAGINAL YEAST INFECTIONS

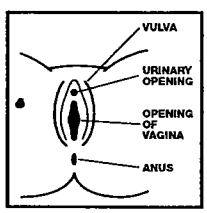
IF THIS IS THE FIRST TIME YOU HAVE HAD VAGINAL ITCH AND DISCOMFORT, CONSULT YOUR DOCTOR. IF YOU HAVE HAD A DOCTOR DIAGNOSE A VAGINAL YEAST INFECTION BEFORE AND HAVE THE SAME SYMPTOMS NOW, USE THIS OINTMENT AS DIRECTED. THIS PRODUCT IS FOR THE TREATMENT OF RECURRENT VAGINAL YEAST INFECTIONS ONLY. IT DOES NOT TREAT OTHER INFECTIONS AND DOES NOT PREVENT PREGNANCY.

This product, a vaginal ointment that contains an antifungal medicine, works to cure most recurrent vaginal yeast infections by killing the overgrowth of yeast.

2 WHAT IS A VAGINAL YEAST INFECTION (*CANDIDIASIS*)?

A yeast infection is caused by an organism called *Candida*, which is a type of yeast. Healthy women usually have this yeast in the vagina. Either an overgrowth or rapid growth of this yeast can cause a vaginal yeast infection. The symptoms of a vaginal yeast infection can include any or all of the following:

- **Vaginal itching** - Itching can range from mild to intense.
- **Vaginal discharge** - This discharge may be thick like paste or lumpy like cottage cheese.
- **Vaginal soreness, burning or irritation** - The vagina can feel sore inside or there can be a burning sensation, particularly during vaginal intercourse.
- **Rash or redness** - Rash or redness may occur around the vagina (vulvar irritation).



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

3 WHAT ARE THE REASONS YOU GET VAGINAL YEAST INFECTIONS?

There are several conditions that can cause too much yeast to grow inside the vagina such as:

- **Hormonal changes** - Changes in hormonal levels can occur during pregnancy, with the use of some birth control pills, and just before a woman's menstrual period.
- **Antibiotics** - Because antibiotics can kill the normal bacteria in the vagina, yeast may grow very quickly.
- **Diabetes** - Diabetes can also make a woman more likely to get a vaginal yeast infection.
- **Human Immunodeficiency Virus (HIV)** - 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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4 WARNINGS

- **Do not use if you have abdominal pain, fever (higher than 100°F orally), chills, nausea, vomiting, diarrhea, or foul-smelling discharge. Contact your doctor immediately.**
- **If your symptoms do not improve in 3 days or if you still have symptoms after 7 days, consult your doctor. Your doctor may recommend other treatment, or you may have a condition other than a yeast infection.**
- **If symptoms return within 2 months or if you think you have been exposed to the human immunodeficiency virus (HIV) that causes AIDS, consult your doctor immediately. Recurring yeast infections may be a sign of pregnancy or a serious condition, such as AIDS or diabetes.**
- **Do not use if you are pregnant or think you may be pregnant, have diabetes, a positive HIV test, or AIDS. Consult your doctor.**
- **Do not use tampons while using this medicine. Use sanitary napkins instead.**
- **Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using this product. This product may damage condoms and diaphragms and may cause them to fail. You should wait 3 days after treatment to resume using condoms or your diaphragm.**
- **Do not use in girls under 12 years of age.**
- **Keep this and all drugs out of the reach of children.**
- **This product is for vaginal use only. Do not use in eyes or take by mouth. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-915

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-915

3. NAME AND ADDRESS OF APPLICANT

L.Perrigo Company
515 Eastern Ave.
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge patent 4,062,966 has expired on 12/13/94. The firm indicated that there are no exclusivity periods remaining in effect for the reference listed drug.

5. SUPPLEMENT(s)

Original 6/26/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Tioconazole

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

N/A

9. AMENDMENTS AND OTHER DATES:

N/A

10. PHARMACOLOGICAL CATEGORY

Treatment of recurrent vaginal yeast infections.

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Ointment

14. POTENCY

6.5%

15. CHEMICAL NAME AND STRUCTURE

1-[2-2(2,4-dichlorophenyl)ethyl]-1H-imidazole

16. RECORDS AND REPORTS

17. COMMENTS

Redacted 10

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-915

3. NAME AND ADDRESS OF APPLICANT

L.Perrigo Company
515 Eastern Ave.
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge patent 4,062,966 has expired on 12/13/94. The firm indicated that there are no exclusivity periods remaining in effect for the reference listed drug.

5. SUPPLEMENT(s)

Original 6/26/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Tioconazole

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/14/01

10. PHARMACOLOGICAL CATEGORY

Treatment of recurrent vaginal yeast infections.

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OTC

12. RELATED IND/NDA/DMF(s)

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Ointment

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6.5%

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1-[2-2(2,4-dichlorophenyl)ethyl]-1H-imidazole

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 6/15/01

Supervisor: Kathy Woodland for Paul Schwartz, Ph.D. 6/29/01

cc: ANDA 75-915
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HFD-627/KWoodland/

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F/T by: DJ 7/18/01

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-915

3. NAME AND ADDRESS OF APPLICANT

L.Perrigo Company
515 Eastern Ave.
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge patent 4,062,966 has expired on 12/13/94. The firm indicated that there are no exclusivity periods remaining in effect for the reference listed drug.

5. SUPPLEMENT(s)

Original 6/26/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Tioconazole

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/14/01
Amendment 8/13/01

10. PHARMACOLOGICAL CATEGORY

Treatment of recurrent vaginal yeast infections.

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Ointment

14. POTENCY

6.5%

15. CHEMICAL NAME AND STRUCTURE

1-[2-2(2,4-dichlorophenyl)ethyl]-1H-imidazole

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable - Pending Bio.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 8/22/0

Supervisor: Paul Schwartz, Ph.D.

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-915

3. NAME AND ADDRESS OF APPLICANT

L.Perrigo Company
515 Eastern Ave.
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge patent 4,062,966 has expired on 12/13/94. The firm indicated that there are no exclusivity periods remaining in effect for the reference listed drug.

5. SUPPLEMENT(s)

Original 6/26/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Tioconazole

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/14/01
Amendment 8/14/01
Amendment 9/13/01

10. PHARMACOLOGICAL CATEGORY

Treatment of recurrent vaginal yeast infections.

11. Rx or OTC

OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Ointment

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6.5%

15. CHEMICAL NAME AND STRUCTURE

1-[2-2(2,4-dichlorophenyl)ethyl]-1H-imidazole

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: /S/ DATE COMPLETED: 9/18/01

Nashed E. Nashed, Ph.D. 9/14/01

Supervisor: James M. Fan 9/15/01

cc: ANDA 75-915
Division File
Field Copy

Endorsements:
HFD-600/N.Nashed/ /S/ 9/18/01
HFD-623/J.Fan/ /S/ 9/18/01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-915

STATISTICAL REVIEW(S)

Statistical Report: L. Perrigo Company, Tioconazole 6.5% Vaginal Ointment; Office of Generic Drugs; ANDA 75-915

OGD reviewer: Mary M. Fanning, MD, Ph.D.

This was a double-blind, randomized, two-treatment, parallel-group study in 369 patients with vulvovaginal candidiasis. The purpose of the study was to show the therapeutic equivalence between the test product, L. Perrigo Company, tioconazole 6.5% vaginal ointment and the reference product, Bristol-Myers Squibb Company, Vagistat®-1, 6.5% vaginal ointment.

Study Design

This was a two-arm parallel double-blind study in patients with vulvovaginal candidiasis. The two products were the test product, L. Perrigo Company, tioconazole 6.5% vaginal ointment given as a single dose or the reference product, Bristol-Myers Squibb Company, Vagistat®-1, 6.5% vaginal ointment.

A total of 369 patients were enrolled and randomly assigned to two treatment groups in the study. At the visit 1 (Day 1), the samples for KOH wet mount and culture for T. vaginalis and yeast were collected. The severity of clinical signs and symptoms (itching, burning/irritation, vulvar/vaginal erythema, vulvar/vaginal edema, vulvar/vaginal excoriation, and vaginal discharge) was evaluated by using a score (0-3, none-severe). The patient was eligible for the study if she had presence of vulvovaginal candidiasis infection confirmed by observation of pseudohyphae in vaginal secretions (10% KOH wet mount) and moderate signs and symptoms score (2+ for each score and 4+ for total scores). The eligible patient was instructed to insert one applicator of the ointment intra vaginally once at bedtime on day 1. The mycological evaluation (KOH and culture) and clinical evaluation (signs and symptoms) were performed at visit 2 (Day 7-10, one week after treatment), and visit 3 (Day 26-32, 4 weeks after the treatment).

Outcome Variables

The primary efficacy variable was therapeutic cure. The second efficacy variables were mycological cure and clinical cure (assessed independently).

In the sponsor's report, the mycological cure and clinical cure were analyzed at visit 2 and visit 3 separately. The therapeutic cure was defined as mycological cure at visit 2 and 3 plus clinical cure at visit 3 only.

The FDA medical office's note: *There is some confusion in the study report concerning the definition of Clinical, Mycological and Therapeutic Cure. It is defined as being based on data from both visit 2 and visit 3. However, the sponsor indicates in another part of the report that determination of bioequivalence will be based on results from visit 3 only. The correct definition includes observations derived from both the post-treatment visits.*

Our criteria were based on the FDA's current evaluability criteria in consultation with the Medical Officer.

Mycological Cure means a negative KOH wet mount and negative vaginal fungal culture at both post-treatment visits.

Clinical Cure is defined as resolution or improvement of clinical signs and symptoms at visit 2 and resolution at visit 3 with no appearance of new symptoms.

Therapeutic Cure is defined as both a clinical and mycological cure.

Statistical Analysis Methods

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between test and reference treatment should be contained within -.20 to .20 in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R \leq -.20$

or $p_T - p_R \geq .20$

versus

H_A: $-.20 < p_T - p_R < .20$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment

Let n_T = sample size of test treatment n_R = sample size of reference treatment

and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Wald interval with Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

H_0 is rejected if $L > -.20$ and $U < .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of two products.

We analyzed the data for equivalence for mycological cure rate, clinical cure rate, and therapeutic cure rate derived from the criteria defined by the FDA medical officer. We also analyzed the same cure rates as those in the sponsor's report.

Statistical Analysis Results

Two analysis populations were defined in the protocol and the sponsor's report:

Modified intent-to-treat (MITT) – All patients who were randomized to drug treatment and were positive for C. albicans and negative for T. vaginalis were included in the MITT set.
Per protocol (PP) – All patients who were in the MITT set and who completed the study according to the protocol (completed all 3 study visits) were included in the PP set.

Based upon the original data set submitted by the sponsor, the modified intent-to-treat population (MITT) included 223 patients randomized to treatment and the per protocol population (PP) was reduced to 211 patients (see medical report for exclusion reasons).

The FDA medical officer's notes[1]:

1) *The patients #367, 8, 43, 51, 265, 198, 155, 317, and 336 should be excluded from the PP population due to outside of the visit windows specified in the protocol and study report.*
2) *Patients who needed to take an additional vulvovaginal or systemic anti-fungal therapy should be considered evaluable and listed as treatment failures. This applies to the following patients: Tioconazole - #83, 254, Vagistat - #9, 28, 152, 376. In addition, two patients (#336 and 337) took Cipro during the follow-up period and they should be excluded from the PP population.*
3) *On evaluation of the data using the stated endpoint under clinical cure, the following patients were changed from the sponsor's determination of cure to failure: Tioconazole – 23, 52, 60, 83, 123, 128, 160, 181, 187, 191, 195, 230, 232, 254, 274, 276, 313, 321, 338, 356, and 367, Vagistat – 28, 31, 131, 133, 135, 148, 152, 168, 259, 314, and 376. In addition, Vagistat patient 354 was changed from the sponsor's determination of failure to cure.*

The data set was adjusted based upon these notes. Consequently, the analyses were performed for adjusted intent-to-treat population (AITT) and adjusted per-protocol population (APP).

APPEARS THIS WAY
ON ORIGINAL

[1] The data set submitted by the sponsor contained very limited information. The adjustment for the original data set was based on the medical reviewer's report and hand notes. There are some differences between the medical report and hand notes. The medical reviewer's hand notes represented the most update information.

The following table shows the population per arm.

Population	Tioconazole	Vagistat	Total
Safety (randomized)	183*	185	368*
Original data set MITT	114	109	223
PP	108	103	211
Adjusted data set AITT	114	109	223
APP	105	96	201

*: A total of 369 patients (184 in the tioconazole group) were randomized to receive treatments. Patient #42 did not take her dose and was subsequently dropped from the study and excluded from all patient populations.

Our analyses used the cure rates derived from the criteria defined by the FDA medical officer for the AITT and APP populations based on the adjusted data set. Additionally, our analyses used the same cure rates as those in the sponsor's report for the MITT and PP populations based on the original data set.

Equivalence analysis

The results of the equivalence analyses are summarized in Table 1 for the AITT and APP populations, and Table 2 for the MITT and PP populations.

The equivalence test was passed for three cure rates using the criteria defined by the FDA medical officer for the AITT and APP populations. The equivalence test was passed for the cure rates used in the sponsor's report for the MITT and PP populations.

Safety

No serious adverse events were reported and no patient discontinued the study as a result of an adverse event in this study. The most common events were vaginitis, vulvoaginitis, vaginal itching, and headache.

Comments on the Sponsor's Equivalence Analyses

The sponsor performed the equivalence analyses for the MITT and PP populations. The mycological cure and clinical cure were analyzed at visit 2 and visit 3 separately. The therapeutic cure was defined as mycological cure at visit 2 and 3 plus clinical cure at visit 3 only. Although the sponsor mentioned that the 90% confidence intervals were computed for the difference between the test and reference cure rates in their protocol and report, there was no detailed description or formula showing how to calculate this confidence interval. The confidence intervals computed by using Wald interval with or without Yates correction could not match sponsor's results. However, the difference was not significant. The sponsor's results were put in Table 2.

Conclusion

Equivalence: The equivalence test was passed for therapeutic cure, mycological cure and clinical cure using the criteria defined by the FDA medical officer for the AITT and APP populations based on the adjusted data set. The equivalence test was passed for therapeutic cure, mycological cure and clinical cure used the criteria defined in the sponsor's report for the MITT and PP populations based on the original data set.

/S/ 6/1/01

Huaixiang Li, Ph.D.
Mathematical Statistician, QMRS

/S/ 6/1/01

Stella Machado, Ph. D.
Director, QMRS

cc:
HFD-615 Harvey Greenberg
HFD-655 Mary Fanning
HFD-705 Stella Machado
HFD-705 Huaixiang Li
HFD-705 QMRS Chron

APPEARS THIS WAY
ON ORIGINAL

Table 1: Equivalence analysis – cure rates based on the criteria defined by the FDA Medical Officer Adjusted data set

Group	Tioconazole No. cured (%)	Vagistat No. cured (%)	Lower CL	Upper CL	Pass/Fail
Adjusted intent-to-treat population (AITT)	(N=114)	(N=109)			
Mycological cure[1]	75 (65.8)	69 (63.3)	-0.089	0.139	P
Clinical cure[2]	53 (46.5)	54 (49.5)	-0.15	0.089	P
Therapeutic cure[3]	42 (36.8)	43 (39.4)	-0.142	0.09	P
Adjusted per-protocol population (APP)	(N=105)	(N=96)			
Mycological cure[1]	72 (68.6)	62 (64.6)	-0.08	0.159	P
Clinical cure[2]	53 (50.5)	51 (53.1)	-0.152	0.099	P
Therapeutic cure[3]	42 (40.0)	40 (41.7)	-0.141	0.107	P

Mycological cure[1] = mycological cure at visit 2 and 3.
Clinical cure[2] = clinical cure at visit 2 and 3.
Therapeutic cure[3] = mycological cure and clinical cure at visit 2 and 3.

Table 2: Equivalence analysis – cure rates based on the criteria used in the sponsor's report*
Original data set

Group	Tioconazole No. cured (%)	Vagistat No. cured (%)	Lower CL	Upper CL	Pass/Fail
Modified intent-to-treat population (MITT) Visit 2	(N=114)	(N=109)			
Mycological cure	101 (88.6)	87 (79.8)	-0.001 *0.000*	0.177 *0.146*	P
Clinical cure	94 (82.5)	87 (79.8)	-0.069 *-0.079*	0.122 *0.083*	P
Visit 3					
Mycological cure	79 (69.3)	77 (70.6)	-0.123 *-0.089*	0.097 *0.111*	P
Clinical cure	76 (66.7)	73 (67.0)	-0.116 *-0.081*	0.11 *0.125*	P
Therapeutic cure [1]	63 (55.3) *65 (57.0)*	55 (50.5) *58 (53.2)*	-0.071 *-0.051*	0.167 *0.171*	P
Per-protocol population (PP) Visit 2	(N=108)	(N=103)			
Mycological cure	98 (90.7)	87 (84.5)	-0.021 *-0.002*	0.147 *0.144*	P
Clinical cure	92 (85.2)	87 (84.5)	-0.084 *-0.074*	0.098 *0.088*	P
Visit 3					
Mycological cure	79 (73.1)	74 (71.8)	-0.098 *-0.088*	0.124 *0.114*	P
Clinical cure	76 (70.4)	72 (69.9)	-0.108 *-0.099*	0.118 *0.109*	P
Therapeutic cure [1]	63 (58.3) *65 (60.2)*	55 (53.4) *57 (55.3)*	-0.072 *-0.063*	0.171 *0.161*	P

*: The *italic* numbers represented the results in the sponsor's report that were different from ours.
Therapeutic cure [1] = Mycological cure at visit 2 and 3 and clinical cure at visit 3.

Statistical Report: L. Perrigo Company, Tioconazole 6.5% Vaginal Ointment; Office of Generic Drugs; ANDA 75-915
Requestor: Mary M. Fanning, MD, Ph.D.

Additional Analysis

Background

This was a double-blind, randomized, two-treatment, parallel-group study in 369 patients with vulvovaginal candidiasis. The purpose of the study was to show the therapeutic equivalence between the test product, L. Perrigo Company, tioconazole 6.5% vaginal ointment and the reference product, Bristol-Myers Squibb Company, Vagistat®-1, 6.5% vaginal ointment.

The original statistical review was finished on June 1, 2001. The equivalence test was passed for therapeutic cure, mycological cure and clinical cure using the criteria defined by the FDA medical officer for the AITT and APP populations based on the adjusted data set. The equivalence test was passed for therapeutic cure, mycological cure and clinical cure used the criteria defined in the sponsor's report for the MITT and PP populations based on the original data set.

The Division of Scientific Investigations conducted an inspection at clinical site #1 (4/25-5/3/01), #10 (6/26-28/01) and #15 (6/13-18/01). The inspection had several concerns that arose from the visit. This additional analysis was performed in response to Dr. Mary Fanning's request on August 2, 2001.The statistical reviewer was advised to exclude patients #86 and 87 from the adjusted intent-to-treat population (AITT) and adjusted per-protocol population (APP) for the equivalence analysis.

Statistical Analysis

The additional analysis used the same cure rates derived from the criteria defined by the FDA medical officer and the equivalence test method as those in the original statistical report.

The results of the additional equivalence analysis are summarized in the following table for the readjusted AITT and APP populations.

Equivalence analysis – cure rates based on the criteria defined by the FDA Medical Office Re-adjusted data set

Group	Tioconazole No. cured (%)	Vagistat No. cured (%)	Lower CL	Upper CL	Pass/Fail
Readjusted intent-to-treat population (RAITT)	(N=113)	(N=108)			
Mycological cure[1]	75 (66.4)	69 (63.9)	-0.09	0.139	P
Clinical cure[2]	53 (46.9)	54 (50.0)	-0.151	0.089	P
Therapeutic cure[3]	42 (37.2)	43 (39.8)	-0.143	0.09	P
Readjusted per-protocol population (RAPP)	(N=104)	(N=95)			
Mycological cure[1]	72 (69.2)	62 (65.3)	-0.08	0.159	P
Clinical cure[2]	53 (51.0)	51 (53.7)	-0.154	0.099	P
Therapeutic cure[3]	42 (40.4)	40 (42.1)	-0.142	0.108	P

Mycological cure[1] = mycological cure at visit 2 and 3.
Clinical cure[2] = clinical cure at visit 2 and 3.
Therapeutic cure[3] = mycological cure and clinical cure at visit 2 and 3.

Conclusion

The equivalence test was passed for therapeutic cure, mycological cure and clinical cure using the criteria defined by the FDA medical officer for the readjusted intent-to-treat (RAITT) and readjusted per-protocol (RAPP) populations.

/S/ 8/10/01
Huaixiang Li, Ph.D.
Mathematical Statistician, QMRS

/S/ 8/10/01
Stella Machado, Ph. D.
Director, QMRS

cc:
HFD-615 Harvey Greenberg
HFD-655 Mary Fanning
HFD-705 Stella Machado
HFD-705 Huaixiang Li
HFD-705 QMRS Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-915

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-915 SPONSOR : PERRIGO

DRUG AND DOSAGE FORM : Tioconazole Vaginal Ointment

STRENGTH(S) : 6.5%

TYPES OF STUDIES : Clinical end point study

CLINICAL STUDY SITE(S) : See Review

ANALYTICAL SITE(S) :

STUDY SUMMARY : A bioequivalence study of the relative clinical efficacy of two 6.5% Tioconazole Vaginal Ointment Products .

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status: completed	Inspection results: acceptable
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other __x___		

PRIMARY REVIEWER : Mary Fanning , M.D. BRANCH : II

INITIAL : /S/ DATE : 8/29/01

TEAM LEADER : S. P. Nerurkar, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 8/28/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 8/28/01

JUL 18 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-915 APPLICANT: L.Perrigo Company

DRUG PRODUCT: Tioconazole 6.5% Vaginal Ointment

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

In order to assist you in future submission please consider the following comments:

1. Please refer to The Draft Guidance for Vulvovaginal Candidiasis - Developing Antimicrobial Drugs for Treatment as well as the Draft Guidance for Industry - Bioequivalence Studies with Clinical Endpoints for Vaginal Antifungal Drug Products in planning future studies for generic vaginal products.

2. The usual criteria for inclusion are "Clinical signs and symptoms of itching, burning/irritation, vulvar erythema/edema, vaginal erythema/edema and vaginal discharge. Presence of at least 2 of these signs or symptoms at a moderate (or greater) score (2+ or greater) are required for inclusion into the study (total score=4+ or greater)." These criteria were listed in the protocol for this study but different criteria were described in the study report. Changes made to protocol definitions should be accompanied by explanations. This study was analyzed using the protocol defined inclusion criteria. All patients met these criteria.

3. Thirteen patients in the Tioconazole group and 15 in the Vagistat® group were outside of the visit windows specified in the protocol and study report. This was attributed to difficulty scheduling patients during the holiday season. All of these patients were included in the per protocol population.

   A Test-of-Cure visit window of 21 to 30 days should be used. The V3 window has been expanded to accommodate holidays and weekends. The OOW subjects that were outside the V3 window specified above were excluded from the Per Protocol population.

4. Patients who needed to take an additional vulvovaginal or systemic anti-fungal therapy were considered evaluable and listed as treatment failures rather than being excluded from the analysis. Patients who received antibiotic therapy were excluded from the analysis.

5. There was some confusion in the study report concerning the definition of Clinical, Mycological and Therapeutic Cure. It was defined as being based on data from both Visit 2 and Visit 3. However, another part of the report indicated that determination of bioequivalence was based on results from Visit 3 only. The correct definition includes observations derived from both the post-treatment visits.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

7/31

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-915

ADMINISTRATIVE DOCUMENTS

APPROVAL PACKAGE SUMMARY FOR 75-915

ANDA: 75-915

FIRM: L.Perrigo Company

DRUG: Tioconazole

DOSAGE: Ointment

STRENGTH: 6.5%

CMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 6/11/01

BIO STUDY/BIOEQUIVALENCE: Bio is acceptable 8/28/01

METHOD VALIDATION: The firm responses to the FDA district laboratories comments is satisfactory 8/29/01

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40°C/75%RH and 24 months room temperature stability data at 25°C/60%RH. The stability samples were stored on their sides.

LABELING REVIEW STATUS: Labeling is satisfactory ~~6/4/01~~ 10/23/01

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing process for the intended production batch for ——— Also, submitted a copy of the exhibit batch lot #8AH80V ———. The firm will use the same drug substance manufacturer, same equipment and same process.

COMMENTS: The application is approvable.

REVIEWER: Nashed E. Nashed, Ph.D. /S/ DATE: 9/14/01 9/18/01

SUPERVISOR: James M. Fan /S/ DATE: 9/15/01 9/18/01

V

APPROVAL PACKAGE SUMMARY FOR 75-915

ANDA: 75-915

FIRM: L.Perrigo Company

DRUG: Tioconazole

DOSAGE: Ointment

STRENGTH: 6.5%

CMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 6/11/01

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METHOD VALIDATION: The firm responses to the FDA district laboratories comments is satisfactory 8/29/01

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40°C/75%RH and 24 months room temperature stability data at 25°C/60%RH. The stability samples were stored on their sides.

LABELING REVIEW STATUS: Labeling is satisfactory ~~6/4/01~~ 10/23/01

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing process for the intended production batch for ——— Also, submitted a copy of the exhibit batch lot #8AH80V ——— The firm will use the same drug substance manufacturer, same equipment and same process.

COMMENTS: The application is approvable. /S/

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 9/14/01 9/19/01

SUPERVISOR: James M. Far... /S/ 9/15/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-915

CORRESPONDENCE

PERRIGO®

September 13, 2001

TELEPHONE AMENDMENT – CHEMISTRY

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC to Fax

Re: Tioconazole Vaginal Ointment, 6.5%
ANDA 75-915

Via facsimile and Federal Express

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-915, Tioconazole Vaginal Ointment, 6.5%, filed on June 26, 2000. Further reference is made to the Chemistry Fax Amendments filed on February 14, 2001, and August 13, 2001. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to submit revised drug substance specifications as requested by Dr. Nashed Nashed, Chemistry Reviewer, on September 4, 2001. This communication is classified as a telephone amendment as designated in the September 4, 2001, telephone conversation.

Comment

Please revise your drug substance specifications to tighten the limit for total related compounds. The limit is too high based on your data.

Response to Comment

The drug substance specification for total related compounds has been tightened from

To support the revised specification for total related compounds of , data for Perrigo testing of six lots of tioconazole are presented in Attachment 1.

A revised blank Perrigo specification for tioconazole may be found in Attachment 2.

The of tioconazole, , is planning to include the revised specification in a future DMF amendment.

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 14 2001

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

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

Please contact me by telephone at (616) 686-1920, by fax at (616) 673-7655, or by mail at the address listed on this letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
ANDA Regulatory Affairs Project Manager

Enclosures

PERRIGO®

August 13, 2001

FAX AMENDMENT – CHEMISTRY

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC to Fax
Acknowledged
NAI/S/
8/16/01

Re: Tioconazole Vaginal Ointment, 6.5%
ANDA 75-915

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-915, Tioconazole Vaginal Ointment, 6.5%, filed on June 26, 2000. Further reference is made to the Chemistry Fax Amendment which was filed on February 14, 2001. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address comments in a facsimile from the Division of Chemistry dated July 23, 2001(Attachment 1). This communication is classified as a FAX AMENDMENT as designated in the July 23, 2001, letter.

A. CHEMISTRY DEFIENCIES

Deficiency 1

Please revise your drug substance specifications to tighten the total related compounds based on your results.

Response to Deficiency 1

Based on previous data, the specification for total related compounds has been tightened from ——— A revised Perrigo specification for tioconazole may be found in Attachment 2.

The —— of tioconazole ——— , is planning to include the revised specification in a future DMF amendment.

Deficiency 2

The packaging interchangeability protocol (p. 358) is not acceptable at this time. Please delete.

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RECD
AUG 15 2001
OGD

Response to Deficiency 2

A revised stability testing program for tioconazole may be found in Attachment 3. The packaging interchangeability protocol has been deleted.

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

Deficiency 3

Please tighten the viscosity limits for in-process controls, finished drug product and stability.

Response to Deficiency 3

Based on statistical analysis (3 sigma of the mean of previous test results), the viscosity limits have been tightened as follows:

	Previous Specification	Current Specification
In-Process	[redacted]	[redacted]
Finished Product	[redacted]	[redacted]
Stability	[redacted]	[redacted]

Attachment 4 contains revised specifications for in-process product, finished drug product and stability.

B. DISTRICT LABORATORY COMMENTS

Comment 1

The [redacted] test does not state the proper % concentration of the [redacted] standard and Limit of Quantitation standard (LOQ) to match the dilutions directed in the method.

Response to Comment 1

The calculation instructions for Limit of Quantitation (LOQ) on page 4 of Procedure No. 1727 were incorrect. The volume used of the [redacted] should have been [redacted], and the sample concentration should have been [redacted]

Chromatographic Purity Standard

In Procedure No. 1727, the directions state to dilute [redacted] of the Assay Standard to [redacted]

The calculation for Limit of Quantitation (LOQ) incorrectly stated that [redacted] is diluted in [redacted]

Sample Concentration

[redacted]

Directions for Procedure No. 1727 state to dilute [redacted] of the [redacted] sample [redacted]

The calculation for Limit of Quantitation (LOQ) incorrectly stated that the sample concentration is [redacted]

Please note that although the calculation instructions were incorrect, the original LOQ calculation of [redacted] was correct. In addition, all of the data for [redacted] included in the ANDA was correctly reported. Please see the Response to Comment B4.

The procedure has been revised and the errors have been corrected. A summary of all changes to the procedure and a copy of the revised procedure may be found in Attachment 5.

Comment 2

The calculations for total impurities excludes USP related compounds from the total without explanation of why they are excluded.

Response to Comment 2

USP Tioconazole Related Compounds A, B, and C are not degradation compounds and do not need to be quantified.

Please see Attachment 5 for a summary of changes to the procedure and a copy of the revised procedure.

Comment 3

There are no directions for the preparation of a resolution solution in the method.

Response to Comment 3

Directions for the preparation of a resolution solution have been added to the method.

Please see Attachment 5 for a summary of changes to the procedure and a copy of the revised procedure.

Comment 4

The firm declares a standard precision % RSD for [redacted] LOQ standards at [redacted] however, the methods were found to have a [redacted]% RSD, and the LOQ was [redacted]

Response to Comment 4

Due to errors, the calculation instructions for Limit of Quantitation (LOQ) on page 4 of Procedure No. 1727 were incorrect. The volume of the [redacted] should have been [redacted], and the sample concentration should have been [redacted], not [redacted]

Although the calculation instructions were incorrect, the original calculation of 0.05% was correct. The numerator and the denominator were each reduced by a factor of 3, as shown below.

Calculation of Limit of Quantitation (LOQ)
with incorrect volume and incorrect sample concentration:

[redacted]

Calculation of Limit of Quantitation (LOQ)
with correct volume and incorrect sample concentration
(as calculated by Detroit District Laboratory):

[redacted]

Calculation of Limit of Quantitation (LOQ)
with correct volume and correct sample concentration:

[redacted]

Shirley A.L. Ii, Regulatory Program Expert, Detroit District Laboratory, was contacted on July 25, 2001, to discuss this deficiency. Ms. Ii responded on July 26, 2001, that due to the low LOQ, an RSD of [redacted]% is acceptable.

Perrigo will retain the system suitability requirement of LOQ standard RSD [redacted]%.

Please also see Response to Comment B1 and Attachment 5.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response that:

Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

Response

A request for additional information from the Division of Bioequivalence was received on January 22, 2001. A telephone amendment was submitted on February 1, 2001.

Comments from the Division of Bioequivalence were received on July 18, 2001.

C. ADDITIONAL INFORMATION

Three procedures have been revised since the original submission. Copies of these procedures were provided to the Detroit District Laboratory on January 15, 2001. In Attachment 6, please find a summary of procedural changes and a copy of each revised procedure.

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 amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

If you have any questions or require additional information, please contact me by telephone at (616) 686-1920, by fax at (616) 673-7655, or by mail at the address on the letterhead.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
ANDA Regulatory Affairs Project Manager

PERRIGO®

February 14, 2001

FAX AMENDMENT – CHEMISTRY

Gary Buehler, Director
FDA, CDER, Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FA

Re: Tioconazole Vaginal Ointment, 6.5%
ANDA 75-915

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-915, Tioconazole Vaginal Ointment, 6.5%, filed on June 26, 2000. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address comments in a facsimile from the Division of Chemistry dated January 16, 2001(Attachment 1). This communication is classified as a FAX AMENDMENT as designated in the January 16, 2001, letter.

CHEMISTRY DEFIENCIES

Deficiency 1

Please revise your drug substance specifications to include limits for total related compounds and provide the test results.

Response

The drug substance ———————, has added the specification for total related compounds and has amended the Certificate of Analysis for lot number 0997012M (which was used for the manufacture of the exhibit batch), to include test results for total related compounds.

A specification for total related compounds has been added to the Perrigo specification for tioconazole. An amended Perrigo Certificate of Analysis for lot number 1585316, corresponding to ——— lot number 0997012M (which was used for the ——— of the exhibit batch), includes test results for total related compounds.

Documentation may be found in Attachment 2.

Deficiency 2

Please revise your specifications for the finished drug product to include limits for ——— content and provide test results.

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RECD
FEB 16 2001
OGD

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

Response

[redacted] which is added to the formula to [redacted] The limit for [redacted] content was set at greater than [redacted] the validated limit of quantitation (LOQ). Residual [redacted] that is present in an amount greater than the LOQ indicates that the formulation is adequately protected from discoloration. To support the proposed [redacted] acceptance criteria, the exhibit batch was tested after 32 months of room temperature storage and met the specifications for description, viscosity, assay, and

Please see Attachment 3 for the following:

- Procedure 1817, "[redacted] in Tioconazole Ointment by [redacted]
- Validation of the Assay Method for [redacted] in Tioconazole Ointment
- Special Assay Report No. 17391 (to support the proposed [redacted] acceptance criteria)

Specifications for finished drug product have been revised to include limits for [redacted] content. Please see Attachment 4 for revised finished product specifications.

Deficiency 3

Please revise your specifications for stability to include limits for [redacted] content and provide test results.

Response

Specifications for stability have been revised to include limits for [redacted] content; see response to Deficiency 2. Please see Attachment 5 for revised stability specifications.

Deficiency 4

The packaging interchangeability protocol (p. 358) is not acceptable at this time.

Response

The packaging interchangeability protocol located on page 358 of the original submission reads as follows:

[redacted]

Section VI of the stability protocol ("Changes") has been revised to delete the reference to 21 CFR 314.70. Please see Attachment 6. L. Perrigo Company acknowledges that major

changes require a Prior Approval Supplement, moderate changes require a Supplement - Changes Being Effected in 30 Days, and minor changes may be filed in the Annual Report.

Deficiency 5

Please indicate from where and how many samples are taken for [redacted]

Response

Step 23 of the manufacturing card (p. 131 of the original submission) outlines the sampling procedure. While the [redacted] Samples are tested and results are reported on a Certificate of Analysis for In-Process Results (p. 213 of the original submission); see also Attachment 7 for these results.

Deficiency 6

Please conduct the assay test on stability at the top, middle, and bottom of the tubes and explain the multiple data points for assay in stability reports.

Response

Procedure 1494, "Assay and Identification of Tioconazole in Tioconazole Ointment and Raw Material by [redacted] has been revised. Samples will be taken from the top, middle, and bottom of the tube and each sample will be assayed for tioconazole. A copy of the revised procedure may be found in Attachment 8.

In the stability reports, multiple data points for assay at the initial time point were reported because a total of five samples were taken from the beginning, middle, and end of the packaging run and then assayed separately. Routine stability assay is performed on one sample in duplicate. For Project 13280 (lot 8DH56V), the sample taken at the 3 month time point was tested in triplicate instead of duplicate, due to analyst error.

Deficiency 7

Please revise your finished drug product specifications to include test and limits for [redacted]

Response

Finished drug product specifications have been revised to include test and limits for [redacted] Please see Attachment 4 for revised finished product specifications.

Viscosity testing was performed at the time of release and has been included in the revised finished product certificate of analysis for lot numbers 8DH56V and 8DH57V (Attachment 9).

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

Comment 1

The firms referenced in your application should be in compliance with cGMP at the time of approval.

Response

L. Perrigo Company acknowledges that the firms referenced in this application should be in compliance with cGMP at the time of approval.

Comment 2

Your methods validation for the drug product has been submitted for validation by FDA district laboratories.

Response

Methods validation for the drug product has been initiated by the Detroit District Laboratory. Request for samples and documentation was received on January 4, 2001. The request was fulfilled on January 15, 2001.

Comment 3

Your bio study is under review.

Response

A request for additional information from the Division of Bioequivalence was received on January 22, 2001. A telephone amendment was submitted on February 1, 2001.

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 amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

Please contact me by telephone at (616) 686-1920, by fax at (616) 673-7655, or by mail at the address on the letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short
ANDA Regulatory Affairs Project Manager

PERRIGO®

February 1, 2001

BIOEQUIVALENCE TELEPHONE AMENDMENT

Gary Buehler, Director
FDA, CDER, Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Re: Tioconazole Vaginal Ointment, 6.5%
ANDA 75-915

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-915, Tioconazole Vaginal Ointment, 6.5%, filed on June 26, 2000. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to supply additional information as requested by Krista Scardina, Project Manager, in a telephone message to Brian Schuster of Perrigo on January 22, 2001. This communication is classified as a bioequivalence telephone amendment as designated in the January 22, 2001, telephone message.

Additional information was requested as follows:

KOH results for visits 2 and 3

Line listing by patient for
- Mycological cure
- Clinical cure
- Therapeutic cure

Please find enclosed two copies each (hard copy and diskette) of the requested information.

Please contact me by telephone at (616) 686-1920, by fax at (616) 673-7655, or by mail at the address listed on this letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short
Regulatory Affairs Project Manager

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

PERRIGO®

October 12, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER,FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: **Original Abbreviated New Drug Application**
Tioconazole Vaginal Ointment, 6.5%
Over-The-Counter.

ORIG AMENDMENT
N/AB

Dear Mr. Buehler:

The L. Perrigo Company submitted on June 26, 2000, an original abbreviated new drug application ("ANDA") seeking approval to market Tioconazole Vaginal Ointment, 6.5%, that is bioequivalent to the reference listed drug, Vagistat®-1, manufactured by the Bristol-Myers Squibb Company, pursuant to NDA 20-676.

On August 14, 2000, Saundra Middleton of the Division of Bioequivalence requested that we submit the Case Report Forms for the bioequivalence study as a telephone amendment. Perrigo hereby amends the original application to submit the requested case report forms. This is a telephone amendment as indicated by Ms. Middleton in the August 14, 2000 telephone conversation with Shelly Meachum of the Perrigo Company.

Please find enclosed the Case Report Forms for the bioequivalence study. These reports total 11,825 pages and are contained in 23 volumes. Two sets of reports are being submitted; the archival copy is contained in blue jackets and the bioequivalence review copy is contained in orange jackets. Each volume contains a table of contents for the case report forms.

The case report forms are organized by clinical site. Each clinical site is numbered and divided by a numbered tab. A blank, green-colored paper divides individual patient case reports within each clinical site.

Please do not hesitate to contact me directly if you have any questions or comments regarding the enclosed case report forms. I may be reached directly by telephone at (616) 686-1575 or by fax at (616) 673-7655, or you may contact me in writing at the address upon this letterhead.

Respectfully submitted,

Shelly K. Meachum

Shelly K. Meachum, RAC
Regulatory Affairs Project Manager - ANDA

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 17 2000
OGD

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

ANDA 75-915

L. Perrigo Company
Attention: Brian R. Schuster
515 Eastern Avenue
Allegan, MI 49010

SEP 1 2000

Dear Sir:

This letter is a correction to our August 17, 2000 acknowledgment letter. The date of application and the date received acceptable for filing have been changed.

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

NAME OF DRUG: Tioconazole Vaginal Ointment, 6.5%

DATE OF APPLICATION: June 26, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 27, 2000

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

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

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

/S/

for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-915
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/NMahmud, Chief, RSB /S/ date 9/1/00
HFD-615/BFritsch, CSO /S/ 8/28/00 date
Word File
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F/T mjl/8/25/00
ANDA Acknowledgment Letter!

ANDA 75-915

L. Perrigo Company
Attention: Brian R. Schuster
515 Eastern Avenue
Allegan, MI 49010

AUG 17 2000

Dear Sir:

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

Reference is also made to the telephone conversation dated August 14, 2000.

NAME OF DRUG: Tioconazole Vaginal Ointment, 6.5%

DATE OF APPLICATION: June 27, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 28, 2000

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

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

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

/S/

for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-915
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/NMahmud, Chief, RSB /S/ date 8/17/00
HFD-615/BFritsch, CSO /S/ 8/15/00 date
Word File V:\Firmsnz\Perrigo\ltrs&rev\75915.ack
F/T mjl/8/15/00
ANDA Acknowledgment Letter!

PERRIGO®

July 6, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER,FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

75-915
NEW CORRESP
NC 810

RE: **Original Abbreviated New Drug Application**
Tioconazole Vaginal Ointment, 6.5%
Over-The-Counter.

Dear Mr. Buehler:

The L. Perrigo Company submitted on June 26, 2000, an original abbreviated new drug application ("ANDA") seeking approval to market Tioconazole Vaginal Ointment, 6.5%, that is bioequivalent to the reference listed drug, Vagistat®-1, manufactured by the Bristol-Myers Squibb Company, pursuant to NDA 20-676.

Subsequent to filing, it was discovered that the original bioequivalence report sent to us by the CRO was not numbered correctly. Enclosed is a complete and corrected bioequivalence report, in both blue binders for the archival copy and orange binders for the bioequivalence review copy. Perrigo requests that the Agency use these enclosed reports, submitted on July 6, 2000, and disregard the reports sent with the original submission on June 26, 2000.

Please direct any written communications to me at the address on this letterhead. Should you need to contact me directly, I can be reached by telephone at (616) 686-1575 or by fax at (616) 673-7655.

Respectfully submitted,

Shelly K. Meachum

Shelly K. Meachum, RAC
Regulatory Affairs Project Manager - ANDA

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 07 2000
OGD

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

PERRIGO®

75-915

NEW CORRESP
NC

June 27, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER,FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Original Abbreviated New Drug Application**
Tioconazole Vaginal Ointment, 6.5%
Over-The-Counter.

Dear Mr. Buehler:

The L. Perrigo Company submitted on June 26, 2000, an original abbreviated new drug application ("ANDA") seeking approval to market Tioconazole Vaginal Ointment, 6.5%, that is bioequivalent to the reference listed drug, Vagistat®-1, manufactured by the Bristol-Myers Squibb Company, pursuant to NDA 20-676.

Today Perrigo is submitting a diskette containing the bioequivalence study in electronic format and two copies of the Analytical Methods, Section 15 for your review. Both the diskette and the copies of Section 15 are enclosed in this shipment.

see letter dated nodisk to be sent 7/27/2

Please direct any written communications to me at the address on this letterhead. Should you need to contact me directly, I can be reached by telephone at (616) 686-1575 or by fax at (616) 673-7655.

Respectfully submitted,

Tricia Posch FOR/

Shelly K. Meachum, RAC
Regulatory Affairs Project Manager - ANDA

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 28 2000
OGD

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

PERRIGO®

75-915

June 26, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER,FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Original Abbreviated New Drug Application**
Tioconazole Vaginal Ointment, 6.5%. Over-The-Counter.

Dear Mr. Buehler:

The L. Perrigo Company submits today an original abbreviated new drug application ("ANDA") seeking approval to market Tioconazole Vaginal Ointment, 6.5%, that is bioequivalent to the reference listed drug, Vagistat®-1, manufactured by the Bristol-Myers Squibb Company, pursuant to NDA 20-676.

Perrigo is submitting an archival copy in blue binders that contains all the information required in an ANDA, including the full bioequivalence study report. A technical review copy is submitted, in red binders, which contains all the information in the archival copy with the exception of the bioequivalence section (6). A separate copy of the bioequivalence section is provided in orange binders. The complete table of contents is included in each binder.

The diskettes, containing the bioequivalence study in electronic format, will be shipped under separate cover.

Perrigo certifies that, in accordance with 21 CFR 314.94(d)(5), a true copy of the technical sections of this ANDA (including a copy of the form FDA 356h) was sent to the Detroit District Office of the FDA. This "field copy" was contained in a burgundy folder. A copy of the cover letter to the Detroit FDA office is enclosed in this ANDA at section 21.

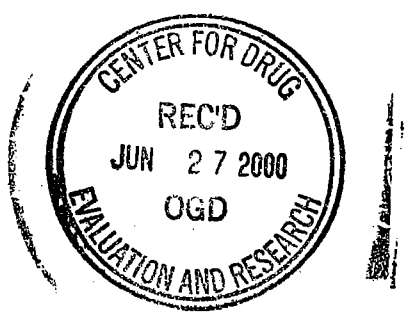
Please direct any written communications to me at the address on this letterhead. Should you need to contact me directly, I can be reached by telephone at (616) 686-1575 or by fax at (616) 673-7655.

Thank you for your prompt handling of this submission.

Respectfully submitted,

Shelly K. Meachum

Shelly K. Meachum, RAC
Regulatory Affairs Project Manager - ANDA



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