CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-953

Name: Terconazole Vaginal Cream, 0.8%

Sponsor: Taro Pharmaceuticals U.S.A., Inc.

Approval Date: April 6, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	
Approved Labeling	X
Labeling Review(s)	X
Medical Review(s)	X
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review(s)	X
Microbiology Review(s)	
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

APPROVAL LETTER

ANDA 75-953

APR 6 2004

Taro Pharmaceuticals U.S.A., Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terconazole Vaginal Cream, 0.8%.

Reference is also made to your amendments dated July 31, 2001; December 3, 2002; and May 21, August 21, and September 4, 2003; and March 22, 2004.

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 labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Terconazole Vaginal Cream, 0.8%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Terazol 3® Vaginal Cream, 0.8%, of Ortho McNeil Pharmaceutical, Inc.).

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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 4/6/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-953
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-620/R.Randad/ RS/randad 3/25/04
HFD-625/S.Liu/ SL 3/26/04
HFD-617/W.Pamphile/ WP 3/25/04
HFD-613/R.Wu/ RWu 3/25/04
HFD-613/J.Grace/ JG 3/29/04

V:\FIRMSNZ\TARO\LTRS&REV\75953.AP.doc
F/T by wp 3/25/04

APPROVAL

AP
3/29/04
per telecon

Robert Lost
4/6/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

APPROVED LABELING

ORIGIN

TERCONAZOLE

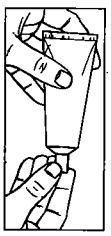
VAGINAL CREAM 0.8%

PATIENT INSTRUCTIONS

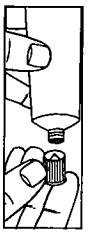
3-DAY THERAPY

Filling the applicator:

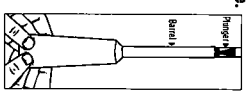
1. Remove the cap from the tube.



2. Use the pointed tip on the top of the cap to puncture the seal on the tube.

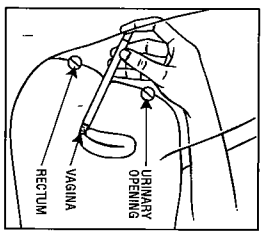


3. Screw the applicator onto the tube.
4. Squeeze the tube from the bottom and fill the applicator until the plunger stops.
5. Unscrew the applicator from the tube.



Using the applicator:

1. Lie on your back with your knees drawn up toward your chest.
2. Holding the applicator by the barrel, insert the filled applicator into the vagina as far as it will comfortably go.



3. Slowly press the plunger of the applicator to release the cream into the vagina.
4. Remove the applicator from the vagina.
5. Apply one applicatorful each night for 3 nights at bedtime, as directed by your doctor.

Cleaning the applicator:

After each use, you should thoroughly clean the applicator by following the procedure below:

1. Pull the plunger out of the barrel.
2. Wash both pieces with lukewarm, soapy water, and dry them thoroughly.

3. Put the applicator back together by gently pushing the plunger into the barrel as far as it will go.

NOTE: Store the cream at controlled room temperature 15° to 30°C (59° to 86°F). See end flap of carton or crimp of tube for lot number and expiration date.

A WORD ABOUT YEAST INFECTIONS

Why do yeast infections occur?

Yeast infections are caused by an organism called *Candida* (KAN di duh). It may be present in small and harmless amounts in the mouth, digestive tract, and vagina. Sometime the natural balance of the vagina becomes upset. This may lead to rapid growth of *Candida*, which results in a yeast infection. Symptoms of a yeast infection include itching, burning, redness, and an abnormal discharge.

Your doctor can make the diagnosis of a yeast infection by evaluating your symptoms and looking at a sample of the discharge under the microscope.

APPROVED
APR - 6 2004

Remove this portion before dispensing

FPO

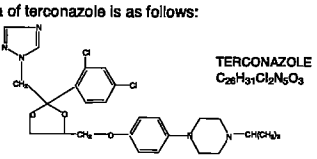
TERCONAZOLE VAGINAL CREAM 0.8%

Rx Only

DESCRIPTION

Terconazole Vaginal Cream 0.8% is a white to off-white, water washable cream for intravaginal administration containing 0.8% of the antifungal agent terconazole, *cis*-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

The structural formula of terconazole is as follows:



TERCONAZOLE
$C_{26}H_{31}Cl_2N_5O_3$

Terconazole, a triazole derivative, is a white to almost white powder with a molecular weight of 532.47. It is insoluble in water; sparingly soluble in ethanol; and soluble in butanol.

CLINICAL PHARMACOLOGY

Following intravaginal administration of terconazole in humans, absorption ranged from 5-8% in three hysterectomized subjects and 12-16% in two non-hysterectomized subjects with tubal ligations.

Following daily intravaginal administration of 0.8% terconazole 40 mg (0.8% cream x 5 g) for seven days to normal humans, plasma concentrations were low and gradually rose to a daily peak (mean of 5.9 ng/mL or 0.006 mcg/mL) at 6.6 hours

Results from similar studies in patients with vulvovaginal candidiasis indicate that the slow rate of absorption, the lack of accumulation, and the mean peak plasma concentrations of terconazole was not different from that observed in healthy women. The absorption characteristics of terconazole 0.8% in pregnant or non-pregnant patients with vulvovaginal candidiasis were also similar to those found in normal volunteers.

Following oral (30 mg) administration of ^{14}C-labelled terconazole, the harmonic half-life of elimination from the blood for the parent terconazole was 6.9 hours (range 4.0-11.3). Terconazole is extensively metabolized; the plasma AUC for terconazole compared to the AUC for total radioactivity was 0.6%. Total radioactivity was eliminated from the blood with a harmonic half-life of 52.2 hours (range 44-60). Excretion of radioactivity was both by renal (32-56%) and fecal (47-52%) routes.

In vitro, terconazole is highly protein bound (94.9%) and the degree of binding is independent of drug concentration.

Photosensitivity reactions were observed in some normal volunteers following repeated dermal application of terconazole 2.0% and 0.8% creams under conditions of filtered artificial ultraviolet light.

Photosensitivity reactions have not been observed in U.S. and foreign clinical trials in patients who were treated with terconazole vaginal cream, 0.8%.

Microbiology: Terconazole exhibits fungicidal activity *in vitro* against *Candida albicans*. Antifungal activity also has been demonstrated against other fungi. The MIC values of terconazole against most *Lactobacillus* spp. typically found in the human vagina were ≥ 128 mcg/mL, therefore these beneficial bacteria are not affected by drug treatment.

The exact pharmacologic mode of action of terconazole is uncertain; however, it may exert its antifungal activity by the disruption of normal fungal cell membrane permeability. No resistance to terconazole has developed during successive passages of *C. albicans*.

INDICATIONS AND USAGE

Terconazole Vaginal Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As Terconazole Vaginal Cream is effective only for vulvovaginitis caused by the genus *Candida*, the diagnosis should be confirmed by KOH smears and/or cultures.

CONTRAINDICATIONS

Patients known to be hypersensitive to terconazole or to any of the components of the cream.

WARNINGS

None.

PRECAUTIONS

General: Discontinue use and do not retreat with terconazole if sensitization, irritation, fever, chills or flu-like symptoms are reported during use.

Laboratory Tests: If there is lack of response to Terconazole Vaginal Cream, appropriate microbiologic studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

Drug Interactions: The levels of estradiol (E2) and progesterone did not differ significantly when 0.8% terconazole vaginal cream was administered to healthy female volunteers established on a low dose oral contraceptive.

How can I prevent yeast infections?

Certain factors may increase your chance of developing a yeast infection. These factors don't actually cause the problem, but they may create a situation that allows the yeast to grow rapidly.

• **Clothing:** Tight jeans, nylon underwear, pantyhose, and wet bathing suits can hold in heat and moisture (two conditions in which yeast organisms thrive). Looser pants or skirts, 100% cotton underwear, and stockings may help avoid this problem.

• **Diet:** Cutting down on sweets, milk products, and artificial sweeteners may reduce the risk of yeast infections.

• **Antibiotics:** Antibiotics work by eliminating disease-causing organisms. While they are helpful in curing other problems, antibiotics may lead to an overgrowth of *Candida* in the vagina.

• **Pregnancy:** Hormonal changes in the body during pregnancy encourage the growth of yeast. This is a very common time for an infection to occur. Until the baby is born, it may be hard to completely eliminate yeast infections. If you believe you are pregnant, tell your doctor.

• **Menstruation:** Sometimes monthly changes in hormone levels may lead to yeast infections.

• **Diabetes:** In addition to heat and moisture, yeast thrives on sugar. Because diabetics often have sugar in their urine, their vaginas are rich in this substance. Careful control of diabetes may help prevent yeast infection.

Controlling these factors can help eliminate yeast infections and may prevent them from coming back.

Some other helpful tips:

1. For best results, be sure to use the medication as prescribed by your doctor, even if you feel better quickly.

2. Avoid sexual intercourse, if your doctor advises you to do so.

3. If your partner has any penile itching, redness, or discomfort, he should consult his physician and mention that you are being treated for a yeast infection.

4. You can use the medication even if you are having your menstrual period. However, you should not use tampons because they may absorb the medication. Instead, use external pads or napkins until you have finished your medication. You may also wish to wear a sanitary napkin if the vaginal medication leaks.

5. Dry the genital area thoroughly after showering, bathing, or swimming. Change out of a wet bathing suit or damp exercise clothes as soon as possible. A dry environment is less likely to encourage the growth of yeast.

6. Wipe from front to rear (away from the vagina) after a bowel movement.

7. Don't douche unless your doctor specifically tells you to do so. Douching may disturb the vaginal balance.

8. Don't scratch if you can help it. Scratching can cause more irritation and spread the infection.

9. Discuss with your physician any medication you are already taking. Certain types of medication can make your vagina more susceptible to infection.

10. Eat nutritious meals to promote your general health.

Mfd. by:
Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1

Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

Revised: May 2003 PK-2311-0

Remove this portion before dispensing

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Studies to determine the carcinogenic potential of terconazole have not been performed.

Mutagenicity: Terconazole was not mutagenic when tested *in vitro* for induction of microbial point mutations (Ames test), or for inducing cellular transformation, or *in vivo* for chromosome breaks (micronucleus test) or dominant lethal mutations in mouse germ cells.

Impairment of Fertility: No impairment of fertility occurred when female rats were administered terconazole orally up to 40 mg/kg/day for a three month period.

PREGNANCY:
Teratogenic Effects:
Pregnancy Category C.
There was no evidence of teratogenicity when terconazole was administered orally up to 40 mg/kg/day (50x the recommended intravaginal human dose of the 0.8% vaginal cream formulation) in rats, or 20 mg/kg/day in rabbits, or subcutaneously up to 20 mg/kg/day in rats.

Dosages at or below 10 mg/kg/day produced no embryotoxicity; however, there was a delay in fetal ossification at 10 mg/kg/day in rats. There was some evidence of embryotoxicity in rabbits and rats at 20-40 mg/kg. In rats, this was reflected as a decrease in litter size and number of viable young and reduced fetal weight. There was also delay in ossification and an increased incidence of skeletal variants.

The no-effect dose of 10 mg/kg/day resulted in a mean peak plasma level of terconazole in pregnant rats of 0.176 mcg/mL which exceeds by 30 times the mean peak plasma level (0.006 mcg/mL) seen in normal subjects after intravaginal administration of terconazole 0.8% vaginal cream. This safety assessment does not account for possible exposure of the fetus through direct transfer to terconazole from the irritated vagina by diffusion across amniotic membranes.

Since terconazole is absorbed from the human vagina, it should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Animal studies have shown that rat offspring exposed via the milk of treated (40 mg/kg/orally) dams showed decreased survival during the first few post-partum days, but overall pup weight and weight gain were comparable to or greater than controls throughout lactation. Because many drugs are excreted in human milk, and because of the potential for adverse reaction in nursing infants from terconazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy in children have not been established.

Geriatric Use: Clinical studies of terconazole 0.8% vaginal cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS
During controlled clinical studies conducted in the United States, patients with vulvovaginal candidiasis were treated with terconazole 0.8% vaginal cream for three days. Based on comparative analyses with placebo and a standard agent, the adverse experiences considered most likely related to terconazole 0.8% vaginal cream were headache (21% vs. 16% with placebo) and dysmenorrhea (6% vs. 2% with placebo). Genital complaints in general, and burning and itching in particular, occurred less frequently in the terconazole 0.8% vaginal cream 3 day regimen (5% vs. 6%-9% with placebo). Other adverse experiences reported with terconazole 0.8% vaginal cream were abdominal pain (3.4% vs. 1% with placebo) and fever (1% vs. 0.3% with placebo). The therapy-related dropout rate was 2.0% for the terconazole 0.8% vaginal cream. The adverse drug experience most frequently causing discontinuation of therapy was vulvovaginal itching 0.7% with the terconazole 0.8% vaginal cream group and 0.3% with the placebo group.

OVERDOSAGE
Overdose of terconazole in humans has not been reported to date. In the rat, the oral LD 50 values were found to be 1741 and 849 mg/kg for the male and female, respectively. The oral LD 50 values for the male and female dog were ≈1280 and ≥ 640 mg/kg, respectively.

DOSAGE AND ADMINISTRATION
One full applicator (5 g) of Terconazole Vaginal Cream (40 mg terconazole) should be administered intravaginally once daily at bedtime for three consecutive days. Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures and other pathogens commonly associated with vulvovaginitis ruled out. The therapeutic effect of Terconazole Vaginal Cream is not affected by menstruation.

HOW SUPPLIED
Terconazole Vaginal Cream 0.8% is available in 20 g tubes with a measured-dose applicator. Store at controlled room temperature 15° to 30°C (59° to 86°F).

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532

May 2003 PK-3438-0

ORIGIN

FPO

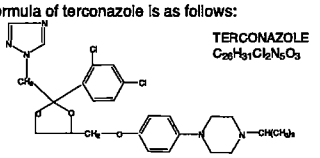
TERCONAZOLE VAGINAL CREAM 0.8%

Rx Only

DESCRIPTION

Terconazole Vaginal Cream 0.8% is a white to off-white, water washable cream for intravaginal administration containing 0.8% of the antifungal agent terconazole, *cis*-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

The structural formula of terconazole is as follows:



Terconazole, a triazole derivative, is a white to almost white powder with a molecular weight of 532.47. It is insoluble in water; sparingly soluble in ethanol; and soluble in butanol.

CLINICAL PHARMACOLOGY

Following intravaginal administration of terconazole in humans, absorption ranged from 5-8% in three hysterectomized subjects and 12-16% in two non-hysterectomized subjects with tubal ligations.

Following daily intravaginal administration of 0.8% terconazole 40 mg (0.8% cream x 5 g) for seven days to normal humans, plasma concentrations were low and gradually rose to a daily peak (mean of 5.9 ng/mL or 0.006 mcg/mL) at 6.6 hours

Results from similar studies in patients with vulvovaginal candidiasis indicate that the slow rate of absorption, the lack of accumulation, and the mean peak plasma concentrations of terconazole was not different from that observed in healthy women. The absorption characteristics of terconazole 0.8% in pregnant or non-pregnant patients with vulvovaginal candidiasis were also similar to those found in normal volunteers.

Following oral (30 mg) administration of ^{14}C-labelled terconazole, the harmonic half-life of elimination from the blood for the parent terconazole was 6.9 hours (range 4.0-11.3). Terconazole is extensively metabolized; the plasma AUC for terconazole compared to the AUC for total radioactivity was 0.6%. Total radioactivity was eliminated from the blood with a harmonic half-life of 52.2 hours (range 44-60). Excretion of radioactivity was both by renal (32-56%) and fecal (47-52%) routes.

In vitro, terconazole is highly protein bound (94.9%) and the degree of binding is independent of drug concentration.

Photosensitivity reactions were observed in some normal volunteers following repeated dermal application of terconazole 2.0% and 0.8% creams under conditions of filtered artificial ultraviolet light.

Photosensitivity reactions have not been observed in U.S. and foreign clinical trials in patients who were treated with terconazole vaginal cream, 0.8%.

Microbiology: Terconazole exhibits fungicidal activity *in vitro* against *Candida albicans*. Antifungal activity also has been demonstrated against other fungi. The MIC values of terconazole against most *Lactobacillus* spp. typically found in the human vagina were ≥ 128 mcg/mL, therefore these beneficial bacteria are not affected by drug treatment.

The exact pharmacologic mode of action of terconazole is uncertain; however, it may exert its antifungal activity by the disruption of normal fungal cell membrane permeability. No resistance to terconazole has developed during successive passages of *C. albicans*.

INDICATIONS AND USAGE

Terconazole Vaginal Cream is indicated for the local treatment of vulvovaginal candidiasis (monilliasis). As Terconazole Vaginal Cream is effective only for vulvovaginitis caused by the genus ***Candida***, the diagnosis should be confirmed by KOH smears and/or cultures.

CONTRAINDICATIONS

Patients known to be hypersensitive to terconazole or to any of the components of the cream.

WARNINGS

None.

PRECAUTIONS

General: Discontinue use and do not retreat with terconazole if sensitization, irritation, fever, chills or flu-like symptoms are reported during use.

Laboratory Tests: If there is lack of response to Terconazole Vaginal Cream, appropriate microbiologic studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

Drug Interactions: The levels of estradiol (E2) and progesterone did not differ significantly when 0.8% terconazole vaginal cream was administered to healthy female volunteers established on a low dose oral contraceptive.

Remove this portion before dispensing

TERCONAZOLE

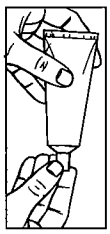
VAGINAL CREAM 0.8%

PATIENT INSTRUCTIONS

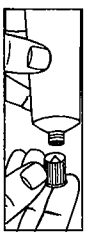
3-DAY THERAPY

Filling the applicator:

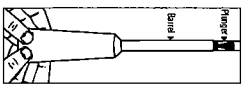
1. Remove the cap from the tube.



2. Use the pointed tip on the top of the cap to puncture the seal on the tube.



3. Screw the applicator onto the tube.
4. Squeeze the tube from the bottom and fill the applicator until the plunger stops.
5. Unscrew the applicator from the tube.

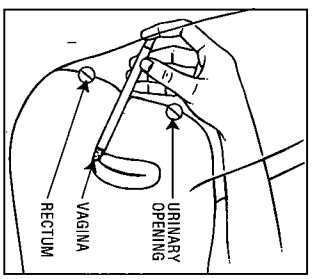


APR - 6 2004

APPROVED

Using the applicator:

1. Lie on your back with your knees drawn up toward your chest.
2. Holding the applicator by the barrel, insert the filled applicator into the vagina as far as it will comfortably go.



3. Slowly press the plunger of the applicator to release the cream into the vagina.
4. Remove the applicator from the vagina.
5. Apply one applicatorful each night for 3 nights at bedtime, as directed by your doctor.

Discard the applicator after each use.

NOTE: Store at controlled room temperature 15° to 30°C (59° to 86°F). See end flap of carton or crimp of tube for lot number and expiration date.

A WORD ABOUT YEAST INFECTIONS

Why do yeast infections occur?

Yeast infections are caused by an organism called *Candida* (KAN di duh). It may be present in small and harmless amounts in the mouth, digestive tract, and vagina. Sometime the natural balance of the vagina becomes upset. This may lead to rapid growth of *Candida*, which results in a yeast infection. Symptoms of a yeast infection include itching, burning, redness, and an abnormal discharge.

Your doctor can make the diagnosis of a yeast infection by evaluating your symptoms and looking at a sample of the discharge under the microscope.

How can I prevent yeast infections?

Certain factors may increase your chance of developing a yeast infection. These factors don't actually cause the problem, but they may create a situation that allows the yeast to grow rapidly.

• **Clothing:** Tight jeans, nylon underwear, pantyhose, and wet bathing suits can hold in heat and moisture (two conditions in which yeast organisms thrive). Looser pants or skirts, 100% cotton underwear, and stockings may help avoid this problem.

• **Diet:** Cutting down on sweets, milk products, and artificial sweeteners may reduce the risk of yeast infections.

• **Antibiotics:** Antibiotics work by eliminating disease-causing organisms. While they are helpful in curing other problems, antibiotics may lead to an overgrowth of *Candida* in the vagina.

• **Pregnancy:** Hormonal changes in the body during pregnancy encourage the growth of yeast. This is a very common time for an infection to occur. Until the baby is born, it may be hard to completely eliminate yeast infections. If you believe you are pregnant, tell your doctor.

• **Menstruation:** Sometimes monthly changes in hormone levels may lead to yeast infections.

• **Diabetes:** In addition to heat and moisture, yeast thrives on sugar. Because diabetics often have sugar in their urine, their vaginas are rich in this substance. Careful control of diabetes may help prevent yeast infection.

Controlling these factors can help eliminate yeast infections and may prevent them from coming back.

Some other helpful tips:

1. For best results, be sure to use the medication as prescribed by your doctor, even if you feel better very quickly.

2. Avoid sexual intercourse, if your doctor advises you to do so.

3. If your partner has any penile itching, redness, or discomfort, he should consult his physician and mention that you are being treated for a yeast infection.

4. You can use the medication even if you are having your menstrual period. However, you should not use tampons because they may absorb the medication. Instead, use external pads or napkins until you have finished your medication. You may also wish to wear a sanitary napkin if the vaginal medication leaks.

5. Dry the genital area thoroughly after showering, bathing, or swimming. Change out of a wet bathing suit or damp exercise clothes as soon as possible. A dry environment is less likely to encourage the growth of yeast.

6. Wipe from front to rear (away from the vagina) after a bowel movement.

7. Don't douche unless your doctor specifically tells you to do so. Douching may disturb the vaginal balance.

8. Don't scratch if you can help it. Scratching can cause more irritation and spread the infection.

9. Discuss with your physician any medication you are already taking. Certain types of medication can make your vagina more susceptible to infection.

10. Eat nutritious meals to promote your general health.

Mfd. by:
Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1

Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

May 2003 PK-3438-0

Remove this portion before dispensing

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Studies to determine the carcinogenic potential of terconazole have not been performed.

Mutagenicity: Terconazole was not mutagenic when tested *in vitro* for induction of microbial point mutations (Ames test), or for inducing cellular transformation, or *in vivo* for chromosome breaks (micronucleus test) or dominant lethal mutations in mouse germ cells.

Impairment of Fertility: No impairment of fertility occurred when female rats were administered terconazole orally up to 40 mg/kg/day for a three month period.

PREGNANCY:
Teratogenic Effects:
Pregnancy Category C.
There was no evidence of teratogenicity when terconazole was administered orally up to 40 mg/kg/day (50x the recommended intravaginal human dose of the 0.8% vaginal cream formulation) in rats, or 20 mg/kg/day in rabbits, or subcutaneously up to 20 mg/kg/day in rats.

Dosages at or below 10 mg/kg/day produced no embryotoxicity; however, there was a delay in fetal ossification at 10 mg/kg/day in rats. There was some evidence of embryotoxicity in rabbits and rats at 20-40 mg/kg. In rats, this was reflected as a decrease in litter size and number of viable young and reduced fetal weight. There was also delay in ossification and an increased incidence of skeletal variants.

The no-effect dose of 10 mg/kg/day resulted in a mean peak plasma level of terconazole in pregnant rats of 0.176 mcg/mL which exceeds by 30 times the mean peak plasma level (0.006 mcg/mL) seen in normal subjects after intravaginal administration of terconazole 0.8% vaginal cream. This safety assessment does not account for possible exposure of the fetus through direct transfer to terconazole from the irritated vagina by diffusion across amniotic membranes.

Since terconazole is absorbed from the human vagina, it should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Animal studies have shown that rat offspring exposed via the milk of treated (40 mg/kg/orally) dams showed decreased survival during the first few post-partum days, but overall pup weight and weight gain were comparable to or greater than controls throughout lactation. Because many drugs are excreted in human milk, and because of the potential for adverse reaction in nursing infants from terconazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy in children have not been established.

Geriatric Use: Clinical studies of terconazole 0.8% vaginal cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS
During controlled clinical studies conducted in the United States, patients with vulvovaginal candidiasis were treated with terconazole 0.8% vaginal cream for three days. Based on comparative analyses with placebo and a standard agent, the adverse experiences considered most likely related to terconazole 0.8% vaginal cream were headache (21% vs. 16% with placebo) and dysmenorrhea (6% vs. 2% with placebo). Genital complaints in general, and burning and itching in particular, occurred less frequently in the terconazole 0.8% vaginal cream 3 day regimen (5% vs. 6%-9% with placebo). Other adverse experiences reported with terconazole 0.8% vaginal cream were abdominal pain (3.4% vs. 1% with placebo) and fever (1% vs. 0.3% with placebo). The therapy-related dropout rate was 2.0% for the terconazole 0.8% vaginal cream. The adverse drug experience most frequently causing discontinuation of therapy was vulvovaginal itching 0.7% with the terconazole 0.8% vaginal cream group and 0.3% with the placebo group.

OVERDOSAGE
Overdose of terconazole in humans has not been reported to date. In the rat, the oral LD 50 values were found to be 1741 and 849 mg/kg for the male and female, respectively. The oral LD 50 values for the male and female dog were ≈1280 and ≥ 640 mg/kg, respectively.

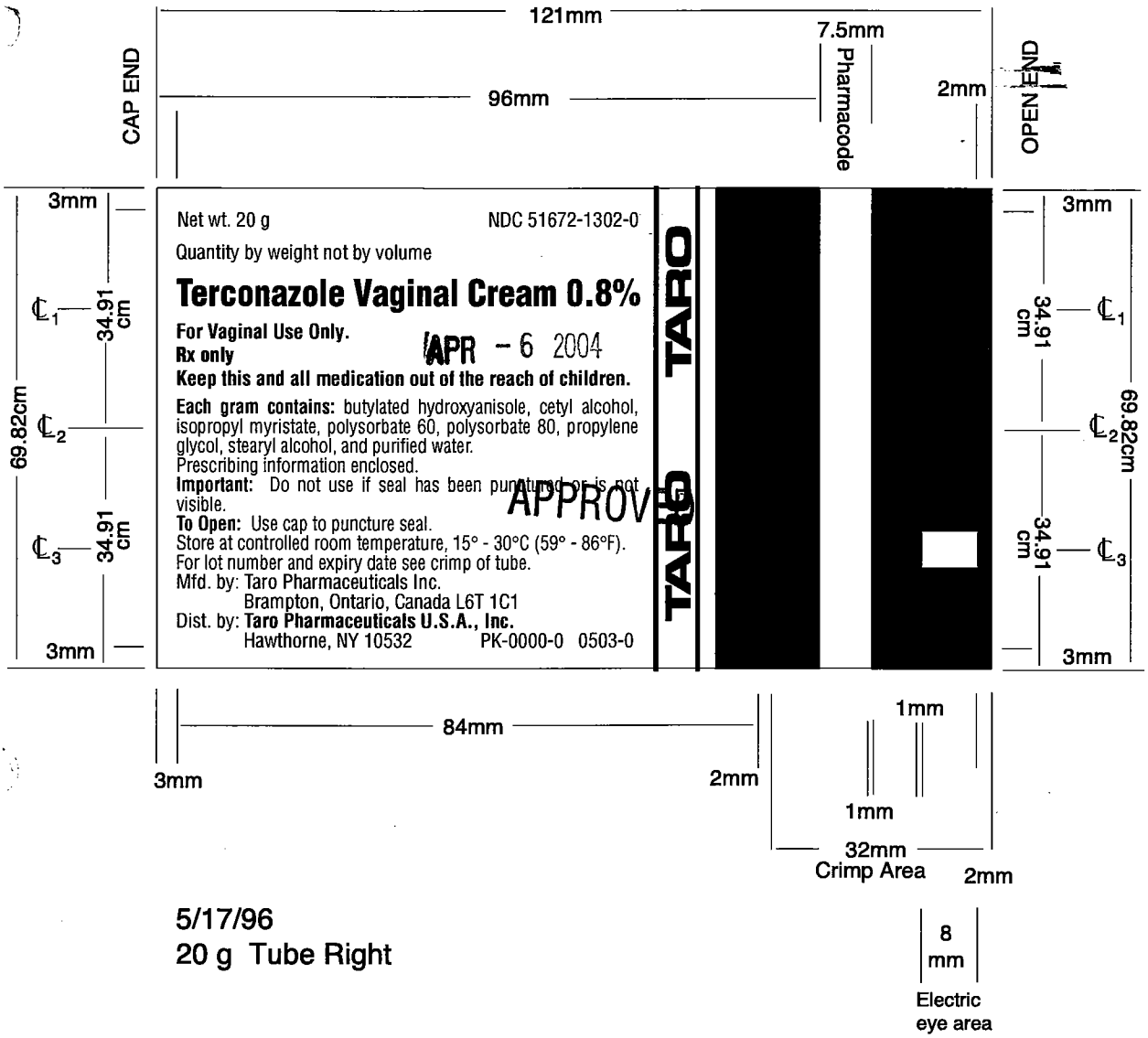
DOSAGE AND ADMINISTRATION
One full applicator (5 g) of Terconazole Vaginal Cream (40 mg terconazole) should be administered intravaginally once daily at bedtime for three consecutive days. Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures and other pathogens commonly associated with vulvovaginitis ruled out. The therapeutic effect of Terconazole Vaginal Cream is not affected by menstruation.

HOW SUPPLIED
Terconazole Vaginal Cream 0.8% is available in 20 g tubes with 3 applicators.
Store at controlled room temperature 15° to 30°C (59° to 86°F).

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532

May 2003 PK-3438-0

ORIGIN



5/17/96
20 g Tube Right

ORIGIN

Each gram contains: butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.
IMPORTANT PATIENT INFORMATION LEAFLET INSIDE
Important: The opening of this product is covered by a safety seal. If this seal has been punctured or is not visible, do not use and return to place of purchase.
To Open: Use top of cap to puncture seal at opening.
Prescribing information enclosed. Store at controlled room temperature, 15° - 30°C (59° - 86°F).
For lot number and expiry date see flap of carton or crimp of tube.

Net wt. 20 g

NDC 51672-1302-0

Terconazole Vaginal Cream 0.8%

Tube and Applicator

For Vaginal Use Only.

APR - 6 2004

APPROVED

Rx only

Keep this and all medication out of the reach of children.

PHARMACIST PLEASE NOTE THE COMBINED INSERT
Unless otherwise instructed by Physician, dispense prescription with Patient Package Insert only. Remove Physician Package Insert at perforation.

Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532

N3 51672 13020 6

TARO

PK-3300-0
0700-0
M000

PMS BLACK

PMS 200

Net wt. 20 g

Terconazole Vaginal Cream 0.8%
Tube and Applicator

Net wt. 20 g

NDC 51672-1302-0

Terconazole Vaginal Cream 0.8%

Tube and Applicator

For Vaginal Use Only.

Rx only

Keep this and all medication out of the reach of children.

TARO

ORIG 1

Each gram contains: butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

IMPORTANT PATIENT INFORMATION LEAFLET INSIDE

Important: The opening of this product is covered by a safety seal. If this seal has been punctured or is not visible, do not use and return to place of purchase.

To Open: Use top of cap to puncture seal at opening.

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

For lot number and expiry date see flap of carton or crimp of tube.

Net wt. 20 g

NDC 51672-1302-0

Terconazole Vaginal Cream 0.8%

Tube and 3 Applicators

APR - 6 2004

APPROVED

For Vaginal Use Only.

Rx only

Keep this and all medication out of the reach of children.

PHARMACIST PLEASE NOTE THE COMBINED INSERT
Unless otherwise instructed by Physician, dispense prescription with Patient Package Insert only. Remove Physician Package Insert at perforation.

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532

Taro is a registered trademark of Taro Pharmaceuticals U.S.A., Inc.

N3 51672 13020 6

TARO

PK-3437-0
0503-0
M000

Net wt. 20 g

NDC 51672-1302-0

Terconazole Vaginal Cream 0.8%

Tube and 3 Applicators

For Vaginal Use Only.

Rx only

Keep this and all medication out of the reach of children.

Net wt. 20 g
Terconazole Vaginal Cream 0.8%
Tube and 3 Applicators

TARO

PMS BLACK

PMS 200

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

LABELING REVIEW(S)

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

ANDA Number: 75-953 Date of Submission: August 31, 2000

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Terconazole Vaginal Cream, 0.8%

Labeling Deficiencies:

1. CONTAINER (20 g) – Satisfactory in draft

2. CARTON (20 g) – Satisfactory in draft

3. INSERT

   a. CLINICAL PHARMACOLOGY – Revise this section to be in accord with approved labeling for this product (Terazol 3 Vaginal Cream – The R.W. Johnson Pharmaceutical Research Institute; approved July 28, 1997) that is attached.

   b. PRECAUTIONS (Pregnancy: Teratogenic Effects) – Revise this subsection to be in accord with the approved labeling for this product that is attached.

4. PATIENT INSTRUCTION SHEET (Cleaning the applicator) – Include a drawing of the separated applicator.

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels: (20 g)
Carton Labeling: (1 x 20 g)
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Terazol 3 Vaginal Cream
NDA Number: 19-964
NDA Drug Name: Terconazole vaginal cream 0.8%
NDA Firm: The R.W. Johnson Pharmaceutical Research Institute
Date of Approval of NDA Insert and supplement #006: July 28, 1997
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: Side-by-side comparison
Basis of Approval for the Carton Labeling: Side-by-side comparison
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. **Labeling review based on the approved labeling for the reference listed drug (Terazol 3 Vaginal Cream (NDA 19-964) – The RW Johnson Pharmaceutical Research Institute; approved July 28, 1997).**

2. **Packaging**
   The RLD packages in product in 20 g tubes.

   Taro is proposing to package its product in 20 g sealed, white [redacted] aluminum tubes with white piercing tips. A reusable plastic applicator is also provided.

3. **Labeling**
   Taro has been asked to revise two sections to be in accord with the approved 1997 labeling. In looking at the side-by-side comparison submitted by the firm, its submission was based on 1995 labeling.

4. **Inactive ingredients**
   There does not appear to be a discrepancy in inactives between the product labeling and the Component and Composition statements.

5. **USP Issues**
   Not a USP item
   RLD – Store at controlled room temperature 15-30°C (59-86°F).
   ANDA – Same as RLD

6. **Bioequivalence Issues – Pending**

7. **Patent/Exclusivity Issues – None**

Date of Review: **February 15, 2001**

Date of Submission: **August 31, 2000**

Primary Reviewer: [signature]

Date: 2/15/01

Team Leader: [signature]

Date: 2/16/2001

cc: ANDA: 75-953
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
\\CDS008\WP51F99\FIRMSNZ\TARO\LTRS&REV\75953na1.l
Review

Superseded by 6/5/03 Apsummary

APPROVAL SUMMARY

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

ANDA Number: 75-953 Date of Submission: May 22, 2001 (Amendment FPL)

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Terconazole Vaginal Cream 0.8%

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: (20 g tube) – Satisfactory as of May 22, 2001 submission (Vol. 2.1, Attachment 13, Page 131)

Carton Labeling:

a. 20 g tube and reusable applicator - Satisfactory as of May 22, 2001 submission (Vol. 2.1, Attachment 13, Page 148)
b. 20 g tube with 3 disposable applicators - Satisfactory as of May 22, 2001 submission (Vol. 2.1, Attachment 13, Page 160)

Professional Package Insert Labeling Combined with Patient Package Insert Labeling:

a. One reusable Applicator - Satisfactory as of May 22, 2001 submission (Code #PK-2311-0, Revised May 2001; Vol. 2.1, Attachment 13, Page 172)
b. Three Disposable applicators – Satisfactory as of May 22, 2001 submission (Code #PK-3438-0, Revised May 2001; Vol. 2.1, Attachment 13, Page 176)

Revisions Needed Post-approval: None

BASIS OF APPROVAL:

Patent Data For NDA 19-964

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired patents.		

Exclusivity Data For NDA 19-964

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity		

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Terazol 3 Vaginal Cream

NDA Number: 19-964

NDA Drug Name: Terconazole Vaginal Cream, 0.8%

NDA Firm: The R.W. Johnson Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplement #006: July 28, 1997

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: Side-by-side comparison

Basis of Approval for the Carton Labeling: Side-by-side comparison

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 contalner label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X

Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. NONE			

NOTE TO THE CHEMIST: Please note that the RLD packages its product with one reusable applicator. However, the applicant is proposing one reusable as well as 3 disposable applicators.

FOR THE RECORD:

1. Labeling review based on the approved labeling for the reference listed drug (Terazol 3 Vaginal Cream (NDA 19-964/S-006) – The RW Johnson Pharmaceutical Research Institute; approved July 28, 1997).

2. Packaging
The RLD packages in product in 20 g tubes with one reusable applicator.

   Taro is proposing to package its product in 20 g sealed, white [redacted] aluminum tubes with white piercing tips. Although the applicator is described as "reusable" in the Container/Closure section of the application, Taro is proposing two packaging configurations: One with a reusable applicator and the other with three disposable applicators as evidenced by the labeling. (Vol 1.4, Section XIII; Page 966)

3. Labeling
Taro revised two sections to be in accord with the approved 1997 labeling as requested.

4. Inactive ingredients
There does not appear to be a discrepancy in inactives between the product labeling and the Component and Composition statements. (Vol. 1.1, Section VII)

5. USP Issues
Not a USP item
RLD – Store at controlled room temperature 15-30°C (59-86°F).
ANDA – Same as RLD

6. Bioequivalence Issues – Pending

Date of Review:	Date of Submission:
June 25, 2001	May 22, 2001 (Amendment)
Primary Reviewer:	Date:
J.W. Golson	6/25/01
Team Leader:	Date:
Debra M. Catterson for John Grace	6/26/01

cc: ANDA: 75-953
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\75953ap.l
Review

****This supercedes the 6/26/01 Approval Summary****
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-953 Date of Submission: May 21, 2003 (Amendment FPL)

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Terconazole Vaginal Cream 0.8%

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: (20 g tube) – Satisfactory as of May 21, 2003 submission (Vol. 4.1)

Carton Labeling:

a. 20 g tube and reusable applicator - Satisfactory as May 21, 2003 submission (Vol. 4.1)
b. 20 g tube with 3 disposable applicators - Satisfactory as of May 21, 2003 submission (Vol. 4.1)

Professional Package Insert Labeling Combined with Patient Package Insert Labeling:

a. One reusable Applicator - Satisfactory as of May 21, 2003 submission (Code #PK-3438-0 & PK-2311-0, Revised May 2003; Vol. 4.1)
b. Three Disposable applicators – Satisfactory as of May 21, 2003 submission (Code #PK-3438-0, Revised May 2003; Vol. 4.1)

Revisions Needed Post-approval: None

BASIS OF APPROVAL:

Patent Data For NDA 19-964

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired patents.		

Exclusivity Data For NDA 19-964

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity		

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Terazol 3 Vaginal Cream

NDA Number: 19-964

NDA Drug Name: Terconazole Vaginal Cream, 0.8%

NDA Firm: The R.W. Johnson Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplement #006: S-011 and S-014; approved March 11, 2003

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: Side-by-side comparison

Basis of Approval for the Carton Labeling: Side-by-side comparison

New RLD labeling approved 9/24/03 (NDA 19-964/S-20). This supplement provides for
① Replacement of reusable applicator with prefilled applicators
② delete all labeling regarding terconazol vaginal suppositories.

These changes do not affect the currently approved labeling for ANDA 75-953 (revised May 2003). I also did a side by side of ANDA 75-953 insert (revised May 2003) with the RLD labeling approved 9/24/03.

Insert labeling ANDA 75-953 Revised May 2003 is still acceptable for approval. Ruby Wu

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. NONE		x	

NOTE TO THE CHEMIST:

FOR THE RECORD:

1. Labeling review based on the approved labeling for the reference listed drug (Terazol 3 Vaginal Cream (NDA 19-964/S-011, S-014) – Johnson & Johnson Pharmaceutical Research & Development, L.L.C; approved March 11, 2003).

Refer to page 1 of review for update. RWu 2/26/04

2. Packaging
The RLD packages in product in 20 g tubes with one reusable applicator.

Taro is proposing to package its product in 20 g sealed, white ——————— aluminum tubes with white piercing tips. Although the applicator is described as "reusable" in the Container/Closure section of the application, Taro is proposing two packaging configurations: One with a reusable applicator and the other with three disposable applicators as evidenced by the labeling. (Vol 1.4, Section XIII; Page 966)

3. Labeling
Taro revised two sections to be in accord with the approved 2003 labeling as requested.

4. Inactive ingredients
There does not appear to be a discrepancy in inactives between the product labeling and the Component and Composition statements. (Vol. 1.1, Section VII)

5. USP Issues
Not a USP item
RLD – Store at controlled room temperature 15-30°C (59-86°F).
ANDA – Same as RLD

6. Bioequivalence Issues – Pending as of June 4, 2003

Date of Review: June 4, 2003 Date of Submission: May 21, 2003 (Amendment)

Primary Reviewer: Ruby Wu RWu Date: 6/5/03 updated 2/26/04

Team Leader: John Grace John Grace Date: 6/5/2003

cc: ANDA: 75-953
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\75953apL2.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
May 16, 2001

ANDA 75-953
Drug Product: Terconazole Vaginal Cream, 0.8%
Sponsor: Taro Pharmaceuticals USA, Inc.
Reference Listed Drug: Terazol® 3 Vaginal Cream, 0.8% (Ortho-McNeil Pharmaceutical)

PURPOSE:

The purpose of this ANDA is to file data on the safety and comparable efficacy in support of the bioequivalence of the generic form of terconazole vaginal cream 0.8% compared to the innovator product, Terazol® 3, Ortho-McNeil Pharmaceutical to obtain approval of the generic form.

Drug Category: Anti-fungal
Dosage form: Vaginal Ointment

BACKGROUND:

Vaginal Candidiasis continues to be one of the most frequent vaginal infections in women of all ages, in the United States. Since the 1970s, it has been successfully treated with the polyenes and the imidazoles. Terconazole is a synthetic triazole ketal derivative antifungal agent, which is clinically indicated for the treatment of vulvovaginal candidiasis. Over the past decade, treatment paradigms for vulvovaginal candidiasis have progressed from seven-day regimens through three-day regimens to a single-dosage treatment for some products. This product was approved in 1991 as a three-day treatment.

OBJECTIVE:

These data are intended to support the claim of bioequivalent safety and efficacy of the generic product, Terconazole vaginal cream, 0.8% (Taro Pharmaceuticals USA, Inc.) given as a three-day treatment and the Reference Listed Drug, Terazol® 3 vaginal cream, 0.8% (Ortho-McNeil Pharmaceutical). The objective of this review is to summarize and evaluate the data from a study submitted by the Applicant in order to reach a conclusion in this regard. This portion of the ANDA contains the results and analysis of a single clinical study that was designed to establish bioequivalence.

STUDY TITLE: A Comparison of the Safety and Efficacy of Two Terconazole 0.8% Vaginal Cream Treatments for Patients with Clinically Symptomatic and Mycologically Confirmed Vulvovaginal Candidiasis.

PROTOCOL NUMBER: TRCZ8-9908

STUDY DATES: February 21, 2000 to July 5, 2000

CRO: Taro Pharmaceuticals, Inc.
Medical Coordinator, Dr. Howard Yanofsky

STUDY OBJECTIVE:

The objective of this study was to demonstrate the bioequivalence of two 3-day treatments for vulvovaginal candidiasis: Terconazole vaginal cream 0.8% manufactured by Taro Pharmaceuticals Inc. and Terazol3® manufactured by Ortho-McNeil U.S.

STUDY DESIGN:

This was a multicenter, parallel group, randomized, double-blind study comparing the following treatments:

- Terconazole vaginal cream, 0.8% (Taro Pharmaceuticals) administered intravaginally once daily for three days and
- Terazol® 3 vaginal cream, 0.8% (Ortho-McNeil Pharmaceutical) administered intravaginally once daily for three days.

INCLUSION/EXCLUSION CRITERIA:

Patients were eligible for entry into the study if they met the following inclusion/exclusion criteria:

Inclusion Criteria

1. Female patients aged 18 years or older.
2. Symptomatic vulvovaginitis. Subsequently, a positive smear (10% KOH wet mount) and a culture positive for *Candida albicans, Candida glabrata (Torulopsis glabrata), Candida parapsilosis,* or *Candida tropicalis* must be demonstrated for the patient to be considered evaluable.
3. Presence of at least one of the following symptoms as assessed by the patient: itching or burning.

4. Presence of at least one of the following clinical signs as assessed by the clinician: vulvar erythema, vulvar edema, vulvar excoriation, vaginal erythema, or vaginal edema.
5. Physical examination within normal limits (excluding vulvovaginal infection) at screening. Minor variations, which are not clinically significant, will be acceptable at the discretion of the investigator.
6. Negative pregnancy test if of child-bearing potential or written consent from obstetrician.
7. Signed informed consent after the study has been fully explained and before any procedures dictated by this protocol are performed.

Exclusion Criteria

Women were to be excluded from the study for any of the following reasons.

1. Pregnancy – first trimester
2. Nursing mother
3. Uncontrolled diabetes mellitus
4. Use currently or within the previous 7 days of the following medications:
   - Oral antibiotics, antifungal, or anti-trichomonal products
   - Topically applied (genital area) antibiotics, antifungals, anti-trichomonal, or anti-inflammatory products
5. Use of any investigational drug within the past 30 days
6. Use of any injectable or oral corticosteroid, immunosuppressive, or immune-stimulating drug within the past 6 months
7. Treatment for candida infection within the previous 3 months
8. Vulvovaginal infection other than candida species. This includes patients with active genital herpes, HPV, bacterial vaginosis, and patients who test positive for: *Trichomonas vaginalis, N. gonorrhea,* or *Chlamydia trachomatis*.
9. Gram stain Nugent score 4 or higher, or diagnosis of bacterial vaginosis
10. History of allergy or sensitivity to Terconazole, or related compounds
11. Recent history of or current clinically significant abnormal liver function studies
12. History of or current drug or alcohol abuse which would affect the patient's ability to follow the protocol

Additional Restrictions were defined in the protocol as follows:

1. Patients will not be permitted to take immunosuppressive drugs or use any oral antibiotics or antifungal agents, or apply any other medications to the affected areas for the 4 weeks of the study. If any of the above medications are used during the study, the patient(s) will be followed under the category of protocol violations.
2. For the first 3 days of the study, patients are to refrain from sexual activities and from using contraceptive creams, foams, or other chemical barriers.

Reasons for Discontinued Participation

Patients were discontinued from the study for the following reasons:

1. Patient's decision to or stated intention to leave the study for any reason.
2. Development of an intercurrent condition or complication which would affect the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the investigator.
3. Ingestion or topical (genital area) application of any intedicted medication.
4. Failure to comply with any aspect of the protocol, including section IV. E or F above.

Medical Officer Note: The last item in the reasons for discontinued participation does not refer to a section that is interpretable in the protocol but instead to this section and the drug administration section. The study report simply states "failure to comply with any aspect of the protocol".

TREATMENT REGIMEN:

Each treatment group was instructed to insert the cream intra-vaginally once at bedtime for 3 days. Patients were individually instructed in the application of the first dose of the cream by the principal investigator or his/her appropriately qualified designee and received an instruction sheet.

The test product was Terconazole 0.8% vaginal cream manufactured by Taro Pharmaceuticals, Inc. (Lot #S172-51910). The reference listed drug product was Terazol® 3 vaginal cream, 0.8% manufactured by Ortho-McNeil Pharmaceutical (Lot 29L466).

STUDY PROCEDURES:

Visit 1 (Day 1)

At the first visit, a medical history and physical were completed and patients underwent laboratory testing, and a urine pregnancy test. Secretions were obtained from the inflamed vaginal wall and the following tests were conducted: a 10% KOH wet mount , a gram stain with Nugent scoring, a wet prep for Trichomonas vaginalis, nucleic acid amplification of Gonorrhea and Chlamydia, and a fungal culture with quantitation and speciation. The severity of clinical signs (vulvar erythema, vulvar edema, vulvar excoriation, vaginal erythema, vaginal edema, and vaginal discharge) was evaluated and recorded using the following scale:

0	=	None
1	=	Slight or mild; minimal
2	=	Moderate; easily discernible
3	=	Moderately severe;
4	=	Severe or extensive.

Medical Officer Note: The study report lists the following signs of vulvovaginal candidiasis (vulvovaginal erythema, edema or excoriation, and discharge) and gives a four point scale for their evaluation: 0=none; 1=mild; 2=moderrate; 3=severe. No explanation was given for these changes.

The severity of symptoms of itching and burning was assessed according to the following scale:

0	=	None
1	=	Mild, causing little discomfort
2	=	Annoying
3	=	Causing marked discomfort
4	=	Marked discomfort causing interference with sleep or activities.

Medical Officer Note: The study report includes itching, burning and irritation as the symptoms for evaluation and gives a four point scale 0=none, 1=mild, 2=moderate, and 3=severe. No explanation was given for these changes. The sponsor should provide an explanation for why the clinical signs were changed and both clinical signs and symptom rating scales were changed and when this change occurred in relation to the study dates.

Informed consent was obtained from eligible patients and study medication and instructions were dispensed. A diary card was provided for the recording of symptoms before taking each dose of study drug and continuing for 7 days.

Visit 2 (Day 14)
Visit 3 (Day 28)

Two (2) and 4 weeks after initiating treatment patients returned for re-evaluation. A gynecologic exam was completed and clinical signs and symptoms were evaluated using the grading scales listed above, A sample was collected for KOH wet mount and fungal culture. Patients were questioned about adverse events. Patients returned the study medication at the 2-week visit. Any study participant experiencing continuing symptoms was encouraged to return at any time for re-evaluation. These patients were considered treatment failures.

Medical Officer Note: No week 2 or week 4 study visit window was defined in the protocol. The protocol made no provisions for evaluation of concomitant medication use or compliance. The study report stipulates that patients were

interviewed regarding the occurrence of adverse events and concomitant illnesses.

The sponsor should be asked to provide their definitions for visit windows and the line listings with the dates of each visit.

PLANNED STATISTICAL EVALUATIONS:

The following definitions were outlined in the protocol:

Mycologic Cure was defined as the proportion of patients with both a negative KOH wet mount and a negative vaginal fungal culture at both post-treatment visits. The study report specified that if a patient had a positive KOH wet mount and/or a positive culture for Candida at either visit 2 or 3, she was counted as a mycologic failure.

Clinical Cure was based on the clinical assessment of erythema, discharge, edema, and excoriation and the patient's report of symptom severity for pruritus and burning at the return visits. The clinical cure rate was defined as a clinical score of 0 or 1 on discharge and a score of 0 on all other signs and symptoms and no other medication or treatment for candidiasis used during the 4 week study period.

Medical Officer Note: The study report modified this definition as follows: Patient had a total symptom score of 0 (discharge was allowed to be a 1) at visit 3. The sponsor should specify why the definition was changes and when during the course of the study this change occurred.

The usual definition of Clinical Cure includes data from both visit 2 and visit 3. Clinical signs and symptoms should have improved at visit 2. At visit 3, the score for any sign or symptom that was a 1 or 2 at baseline should be 0, and any sign or symptom with a baseline score of 3(severe) should be 0 or 1.

Therapeutic Cure was defined as the proportion of patients in each treatment group who had both a clinical and mycologic cure.

The study report included the following additional definitions:

Treatment Failure was defined as patients who were discontinued from the study because of an inadequate clinical or mycologic response and patients who discontinued study drug due to a treatment-related adverse event. These patients were counted as a clinical, mycologic, and therapeutic failure for subsequent visits.

Exclusions were defined as any patient who did not meet the inclusion/exclusion criteria or who had a negative baseline KOH or culture. These patients were excluded at baseline as ineligible.

The protocol specified that the 4-week visit was to be used for the determination of efficacy.

> *Medical Officer Note: Both post-treatment visits should be used for the determination of efficacy. Patients should have a Mycologic Cure at each visit and a Clinical Cure as defined in item #5.*

Patients who did not complete due to persistence of symptoms, treatment failure, or a drug related adverse event were categorized as treatment failures. Patients who did not comply with the protocol were considered protocol violations and were excluded from the analyses. Patients who withdrew for reasons other than treatment failures were excluded from the analyses. Patients who were lost to follow-up were categorized as dropouts and were excluded from the analyses. Excluded patients were replaced to ensure that 80 patients in each group completed the study.

> *Medical Officer Note: The study report should define an Intent-to-Treat population. The Evaluable (or Per Protocol) population should then be defined. If patients were considered failures at visit 2, they should be included in the Evaluable population even if visit 3 data was not available. In this type of study, excluded patients generally are not replaced. Usually, enrollment is higher than the projected sample size for the Evaluable population to ensure that an adequate sample is available for final analysis.*

The protocol indicated that the efficacy comparison to determine if the two treatments were equivalent (i.e., the difference in therapeutic cure rates is less than or equal to 20%) and will employ the two one-sided test procedure (Blackwalder's).

RESULTS:

Enrollment

In total, 170 patients were enrolled between February 21 and June 2, 2000. Of these patients, 84 were randomized to receive Taro's terconazole and 86 to receive Ortho's Terazol®.

Investigators:

The following investigators participated in the study:

Investigators	Study Site Location
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	
Dr.	

Dr. —— did not enroll any patients in the study. There is no information provided about the number of patients enrolled at each site and no analyses were conducted for treatment by center differences.

> *Medical Officer Note: The sponsor should be asked to provide information about the number of patients enrolled at each site and conduct an analysis of treatment by center differences in outcome.*

Populations:

No intent-to-treat population was defined. The Evaluable (Per Protocol) population is defined above.

Thirteen patients were excluded from the Evaluable population. The reasons for exclusion are listed in Table I.

Table I
Reasons for Exclusion from Evaluable Population

Patient Number	Treatment Group	Reason for Exclusion	Sponsor's comments	Medical Officer comments
108	Ortho	Ineligible	Uncontrolled diabetic	
117	Ortho	Excluded	Lab error	No V3 culture, Failure at V2; include
125	Ortho	Drop out	Did not return for V3; was a clinical & mycologic failure at V2	Failure at V2; nugent score of 5; exclude
314	Ortho	Excluded	Lab error	No V3 culture; Cure at V2

618	Ortho	Ineligible	Negative baseline culture	See comment below
710	Ortho	Ineligible	Enrollment culture positive for interdicted organism	Baseline culture positive for C. albicans; Clinical Failure at V2; include
303	Ortho	Protocol Violation	Developed intercurrent condition and stopped study drug	Condition not specified in study report
602	Ortho	Ineligible	On interdicted medication at enrollment and recent episode of vaginal candidiasis	
713	Ortho	Protocol Violation	Returned drug unopened – did not participate	
619	Taro	Ineligible	Negative baseline culture	See comment below
808	Taro	Protocol Violation	Enrollment culture positive for interdicted organisms	
118	Taro	Ineligible	Did not use all study drug	
603	Taro	Ineligible	Recent episode of vaginal candidiasis	

Medical Officer Note: Patient #117 did not have a visit 3 fungal culture and KOH and was excluded as a "Lab error". This patient was a failure at visit 2 and should be included in the final analysis as a therapeutic failure. Patient #710 was excluded because, purportedly, an interdicted organism was reported from the fungal culture. The patient listings report that this patient's fungal culture grew Candida albicans. This patient had a clinical failure at visit 2 and should be included in the final analysis as a failure. The intercurrent condition experienced by patient #303 was not specified in the study report or the line listings. The sponsor should be asked to provide this information.

Medical Officer Note: Only 2 among those excluded had a negative baseline fungal culture. This is an unusually low rate. Generally, all of the women who have a positive KOH smear at the baseline visit are enrolled and receive treatment, pending the results of their fungal culture that is taken at the baseline visit. However, their study eligibility is partly determined by the results of the baseline culture, which is not available at the time of enrollment. Once the results of the fungal culture are available, those with a negative culture are identified as

ineligible. Their data should be included in the Safety population. The usual rate of negative cultures with a positive KOH is approximately 20 to 30%. The sponsor should be asked to provide information about their screening process, the timing of enrollment related to the receipt of a positive fungal culture and why their negative culture rate is so low.

The following was an inclusion criterion in the study protocol: Presence of at least one of the following symptoms as assessed by the patient: itching or burning. The following patients had neither of these symptoms at baseline – number 106, 110, 809, 811, 814, 817, and 1024 (Ortho) and 100, 102, and 1012 (Taro).

1. *Medical Officer Note: The following patients were ineligible because they did not meet the inclusion criterion "Presence of at least one of the following symptoms as assessed by the patient: itching or burning". # 100, 102, 106, 110, 809, 811, 814, 817, 1012, and 1024. They should be excluded from the Evaluable population.*

The following was an exclusion criterion in the study protocol: Gram stain Nugent score 4 or higher, or diagnosis of bacterial vaginosis. The following patients had nugent scores of 4 or higher – number 125, 127, 602, 605, 618, 619, 715, 716, 718, 724, 801, 1007, 1009, 1017, and 1024. Subject # 125 was excluded already from the Evaluable population but for the wrong reason. Subject # 602 was excluded because of a recent vaginal candidiasis infection. Subjects # 618 and 619 were already excluded because of a negative baseline fungal culture.

Medical Officer Note: The following patients were ineligible because they did not meet the exclusion criterion "Gram stain Nugent score 4 or higher, or diagnosis of bacterial vaginosis": #127, 605, 715, 716, 718, 724, 801, 1007, 1009, 1017, and 1024. They should be excluded from the Evaluable population.

Subject #609 had no data for visit 2 and 3 but she is not counted among the exclusions. This subject is included in the Evaluable data set as a Failure.

Medical Officer Note: Subject #609 had no data for visit 2 and 3 but she is not counted among the exclusions. This subject is included in the Evaluable data set as a Failure. The sponsor should be asked to explain why there is no visit 2 or 3 data for this subject and why they are included in the Evaluable population as a failure.

Several subjects who had protocol deviations were included in the Evaluable population. They are described below in Table II.

Table II
Evaluable Patients with Protocol Deviations

Patient Number	Treat ment Group	Protocol Deviations	Medical Officer comments
308	Ortho	Patient 16.5 years old, sexually active*	This patient does not meet inclusion criteria; exclude
316	Ortho	6 days late for visit 3	
1030	Ortho	Patient 17.5 years old, sexually active*	This patient does not meet inclusion criteria; exclude
123	Taro	7 days early for visit 3	
130	Taro	Stopped drug due to adverse event	
609	Taro	Discontinued study due to adverse event	
810	Taro	4 days early for visit 3	

*In Canada, gynecologists are permitted to treat sexually active teenagers without parental consent.

Medical Officer Note: Patients # 308 and 1030 do not meet the inclusion criteria that stipulate that subjects must be 18 years of age or older. They should be excluded from the Evaluable population.

The demographic data at baseline was similar in both treatment groups.

Efficacy results:

The efficacy analysis in this review was based on the evaluability and outcome criteria summarized earlier in this review including the modifications made by the Medical Officer. Table III lists the adjusted efficacy data from this study.

Table III
Mycological, Clinical and Therapeutic Cure Rates

Cure Rates	Ortho N=71	Taro N=60
Mycological Cure	43/71 (60%)	35/60 (58%)
Clinical Cure	47/71 (66%)	40/60 (67%)
Therapeutic Cure	33/71 (46%)	30/60 (50%)
Clinical Cure (new definition of cure)	32/71 (45%)	20/60 (33%)
Therapeutic Cure (new definition of cure)	24/71 (34%)	15/60 (25%)

The 90% confidence interval for the Therapeutic Cure is –12.42, 19.47. The 90% Confidence Interval for the Therapeutic Cure derived using a new definition of Clinical Cure is –23.37, 5,77.

No additional review of the sponsor's analysis or the bioequivalence data will be carried out until the sponsor has responded to the question listed at the end of this document. The sponsor's answers to these questions may alter the final efficacy/bioequivalence analysis.

Safety Results:

The data submitted by the Applicant for safety were reviewed. Those adverse events that were reported by >2% of the population are presented in Table IV and those most frequently related to study drug are presented in Table V.

No serious adverse events were reported in this study. Patient #130 developed an allergic reaction – itching and patient #609 experienced vulvovaginal pruritus and burning. Both subjects discontinued the study as a result of an adverse event. The most common events were headache and upper respiratory infection.

Table IV
Adverse Events Reported by >2% of the Population for Each Treatment Group

Adverse Event	Treatment Group			
	Taro Terconazole (n=84)		OrthoTerazol (n=86)	
	n	%	n	%
Headache	8	9.5	4	5
Vaginal delivery	2	2.4	0	0
Cramping/uterine pain	0	0	2	2.3
Upper Respiratory Infection	5	5.8	3	3.6
Back Pain	2	2.4	0	0

Table V
Adverse Events Most Frequently Reported to be Related to Study Drug

Adverse Event	Treatment Group			
	Taro Terconazole (n=84)		Ortho Terazol (n=86)	
	n	%	n	%
Vulvovaginal pruritus & burning	1	1.2	0	0
Itching (allergic)	1	1.2	0	0
Vaginal pruritus	1	1.2	0	0
Body itching	1	1.2	0	0
Gummy vaginal discharge	0	0	1	1.2
Back pain	2	2.4	0	0

CONCLUSION:

CONCLUSION:

There are numerous issues related to this in vivo bioequivalence study that require clarification by the sponsor. The following comments should be transmitted to the sponsor and answers submitted before a final review can be completed .

1. The study report lists the following signs of vulvovaginal candidiasis (vulvovaginal erythema, edema or excoriation, and discharge) and gives a four point scale for their evaluation: 0=none; 1=mild; 2=moderrate; 3=severe. No explanation was given for these changes. The sponsor should provide an explanation for why the clinical signs and the scale for scoring them was changed and when this change occurred in relation to the study dates.

2. The study report includes itching, burning and irritation as the symptoms for evaluation and gives a four point scale 0=none, 1=mild, 2=moderate, and 3=severe. No explanation was given for these changes. The sponsor should provide an explanation for why the symptom rating scales were changed and when this change occurred in relation to the study dates.

3. No week 2 or week 4 study visit window was defined in the protocol. The protocol made no provisions for evaluation of concomitant medication use or compliance. The study report stipulates that patients were interviewed regarding the occurrence of adverse events and concomitant illnesses. The sponsor should be asked to provide their definitions for visit windows and for compliance and the patient line listings with the dates of each visit as well as the study day for each visit and a list of patients who were outside the study windows.

4. The sponsor did not provide a listing of the number of subjects enrolled at each study site. This information should be provided and an analysis of treatment by center differences in outcome should be conducted.

5. The study report modified the definition of Clinical Cure as follows: Patient had a total symptom score of 0 (discharge was allowed to be a 1) at visit 3. The sponsor should specify why the definition for Clinical Cure was changed and when this change occurred in relation to the study dates.

   The usual definition of Clinical Cure includes data from both visit 2 and visit 3. At visit 2, clinical signs and symptoms should have improved. At visit 3, any sign or symptom that was a 1 or 2 at baseline the score should be 0, and any sign or symptom with a baseline score of 3(severe) should be 0 or 1.

6. Both post-treatment visits should be used for the determination of efficacy. Patients should have a Mycologic Cure at each visit and a Clinical Cure as defined in item #5.

7. The study report should define an Intent-to-Treat population. The Evaluable (or Per Protocol) population should then be defined. If patients were considered failures at visit 2, they should be included in the Evaluable population even if visit 3 data was not available. In this type of study, excluded patients are generally not replaced. Usually, enrollment is higher than the projected sample size for the Evaluable population to ensure that an adequate sample is available for final analysis.

8. Patient #117 did not have a visit 3 fungal culture and KOH and was excluded as a "Lab error". This patient was a failure at visit 2 and should be included in the final analysis as a therapeutic failure. Patient #710 was excluded because, purportedly, an interdicted organism was reported from the fungal culture. The patient listings report that this patient's fungal culture grew Candida albicans. This patient had a clinical failure at visit 2 and should be included in the final analysis as a failure. The intercurrent condition experienced by patient #303 was not specified in the study report or the line listings. The sponsor should be asked to provide this information.

9. Only 2 among those excluded had a negative baseline fungal culture. This is an unusually low rate. Generally, all of the women who have a positive KOH smear at the baseline visit are enrolled and receive treatment, pending the results of their fungal culture that is also taken at the baseline visit. However, their study eligibility is partly determined by the results of the baseline culture, which is not available at the time of enrollment. Once the results of the fungal culture are available, those with a negative culture are identified as ineligible. Their data should be included in the Safety population. The usual rate of negative cultures with a positive KOH is approximately 20 to 30%. The sponsor should be asked to provide information about their screening process, the timing of enrollment related to the receipt of a positive fungal culture and why their negative culture rate is so low.

10. The following patients were ineligible because they did not meet the inclusion criterion "Presence of at least one of the following symptoms as assessed by the patient: itching or burning": # 100, 102, 106, 110, 809, 811, 814, 817, 1012, and 1024. They should be excluded from the Evaluable population.

11. The following patients were ineligible because they did not meet the exclusion criterion "Gram stain Nugent score 4 or higher, or diagnosis of bacterial vaginosis": #127, 605, 715, 716, 718, 724, 801, 1007, 1009, 1017, and 1024. They should be excluded from the Evaluable population.

12. Subject #609 had no data for visit 2 and 3 but she is not counted among the exclusions. This subject is included in the Evaluable data set as a Failure. The sponsor should be asked to explain why there is no visit 2 or 3 data for this subject and why they are included in the Evaluable population as a failure.

13. Patients # 308 and 1030 do not meet the inclusion criteria that stipulate that subjects must be 18 years of age or older. They should be excluded from the Evaluable population.

14. The sponsor was asked to provide a number of case report forms. These have not been received to date. The sponsor should be asked to provide all the patient case report forms.

Mary M. Fanning, MD, Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA # 75-953
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer: Mary Fanning

Endorsements: (Draft and Final with Dates)
HFD-650/Mary Fanning
HFD-650/Rabi Patnaik 5/17/2001
HFD-650/Lizzie Sanchez
HFD-658/Steven Mazzella
HFD-650/Dale Conner 5/24/01

V:\firmsnz\taro\ltrs&rev\75-953

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 31 AUG 2000

5. **Bio Study** (STU) Strengths: 0.8%

Outcome: UN

Outcome Decisions: **UN** - Unacceptable

WinBio Comments: STA - Unacceptable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** **No. 1**

2. **ANDA #** 75-953 [**Terconazole Vaginal Cream, 0.8%**]

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Telephone: (914) 345-9001 FAX: (914) 345-8728

4. **LEGAL BASIS OF SUBMISSION:**
Reference Listed Drug: Terazol® 3
Manufacturer: Ortho Pharmaceutical Corporation (NDA # 19-964)

The applicant has certified that in their opinion and to the best of their knowledge, there are no patents relates to Terazol® 3 and there are no marketing exclusivities currently in effect.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Terconazole Vaginal Cream, 0.8%

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

9. **AMENDMENTS AND OTHER DATES:**
Taro:
08/31/00 Original submission (receive on 08/31/00)
09/21/00 New Correspondence (Re: Bio issue)
09/22/00 Submission of CNC ESD
10/20/00 New correpondence (Re: bio issue)
10/26/00 New correpondence (Re: bio issue)

FDA:
08/31/00 Date Acceptable for filing
10/04/00 Date of acknowledgment letter

10. **PHARMACOLOGICAL CATEGORY:**
Antifungal agent (treatment of local yeast infections)

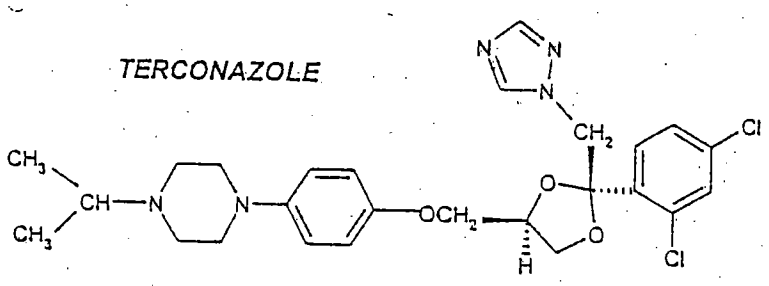
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
NDA: 19-964 (See Item 37 for DMF list and comments).

13. **DOSAGE FORM:** Vaginal cream

14. **POTENCY**: 0.8%

15. **CHEMICAL NAME AND STRUCTURE:**
cis-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
Both the drug substance and the drug product are not listed in the USP 24. Type II DMF of the drug substance is inadequate. There are many CMC deficiencies.

Labeling review and bioequivalence review are pending. No microbiological review is needed.

Acceptable EER has not been received.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (MINOR amendment)

19. **REVIEWER**: Shing H. Liu, Ph.D. **DATE COMPLETED**: 01/25/01

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 75-953
Field Copy
Division File

Endorsements:

HFD-627/S.Liu/01-25-01 S.H.Liu 02/02/01
HFD-627/K. Woodland for P. Schwartz/1/29/01 K Woodland 2/6/01
HFD-619/E. Hu/2/1/01

V:\firmsnz\taro\ltrs&rev\75953cr1.taro\terconazole.ele.doc

F/T by: DJ 2/2/01

Not Approvable (MINOR AMENDMENT)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** **No. 2**

2. **ANDA #** 75-953 [**Terconazole Vaginal Cream, 0.8%**]

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Telephone: (914) 345-9001 FAX: (914) 345-8728

4. **LEGAL BASIS OF SUBMISSION:**
Reference Listed Drug: Terazol® 3
Manufacturer: Ortho Pharmaceutical Corporation (NDA # 19-964)

The applicant has certified that in their opinion and to the best of their knowledge, there are no patents relates to Terazol® 3 and there are no marketing exclusivities currently in effect.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Terconazole Vaginal Cream, 0.8%

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

9. **AMENDMENTS AND OTHER DATES:**
Taro:
08/31/00 Original submission (receive on 08/31/00)
09/21/00 New Correspondence (Re: Bio issue)
09/22/00 Submission of CNC ESD
10/20/00 New correpondence (Re: bio issue)
10/26/00 New correpondence (Re: bio issue)
05/22/01* Amendment (MINOR) [Subject of This Review]
07/03/01* Telephone amendment [Subject of This Review]

FDA:
08/31/00 Date Acceptable for filing
10/04/00 Date of acknowledgment letter
02/21/00 NA (MINOR) letter (based on CR #1 by S. Liu, Ph.D.)

10. **PHARMACOLOGICAL CATEGORY:**
Antifungal agent (treatment of local yeast infections)

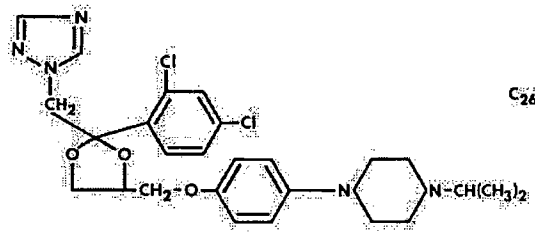
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
NDA: 19-964 and ANDA 76-043 (Terconazole Vaginal Cream, 0.4%)

13. **DOSAGE FORM**: Vaginal cream

14. **POTENCY**: 0.8%

15. **CHEMICAL NAME AND STRUCTURE:**
cis-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
Both the drug substance and the drug product are not listed in the USP 24. Type II DMF of the drug substance is adequate. There are no remaining CMC issues.

Labeling review is pending. Bioequivalence deficiencies have been issued to the applicant. No microbiological review is needed.

Acceptable EER has not been received. See Item 31 for comment on the method validation.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not Approvable (MINOR Amendment)

19. **REVIEWER**: Shing H. Liu, Ph.D. **DATE COMPLETED**: 06/20/01
Revised on 07/18/01

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-953 **APPLICANT:** Taro Pharmaceuticals USA Inc.

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

The deficiencies presented below represent a MINOR deficiency.

Bioequivalence for this drug product has not been established. Please refer to the deficiencies from the Division of Bioequivalence dated June 6, 2001. Please do not respond to this communication until all outstanding Bioequivalence deficiencies have been addressed.

Sincerely yours,

Paul S Lee for 8/1/01

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

cc: ANDA 75-953
Field Copy
Division File

Endorsements:

HFD-627/S.Liu, Ph.D./06/20/01/06-25-01/07-18-01 S.H.Liu 07/27/01
HFD-627/G. Kang for P. Schwartz, Ph.D./07/19-01 GK 7/27/01
HFD-619/T. Ames/07/25/01 for 8/1/01

V:\firmsnz\taro\ltrs&rev\75953cr2.taro\terconazole.ele.doc

F/T by: jg/07/26/01

Not Approvable (MINOR amendment)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** No. 3 (Rev. #1 & 2 by S. Liu)

2. **ANDA #** 75-953 [Terconazole Vaginal Cream, 0.8%]

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Telephone: (914) 345-9001 Ext. 298 FAX: (914) 345-8728

4. **LEGAL BASIS OF SUBMISSION:** 505(J) of the FD&C Act.

5. **SUPPLEMENT(s)/AMENDMENT(s):** 75-953/AMEND

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Terconazole Vaginal Cream, 0.8%

8. **SUPPLEMENT(s)/AMENDMENT(S) PROVIDE(s) FOR:** CMC documentation in support of the new exhibit batch for clinical study.

9. **AMENDMENTS AND OTHER DATES:**

Taro:

08/31/00	Original submission
09/21/00	New Correspondence (Re: Bio issue)
09/22/00	Submission of CNC ESD
10/20/00	New correspondence (Re: bio issue)
10/26/00	New correspondence (Re: bio issue)
05/22/01	Amendment (minor)
07/03/01	Telephone amendment
07/31/01	New correspondence (Re: bio issue)
12/03/02	**New correspondence (subject of this review)**

FDA:

08/31/00	Date Acceptable for filing
10/04/00	Date of acknowledgment letter
02/21/01	NA (minor) [rev. #1 by S. Liu)
06/06/01	bio-correspondence
08/02/01	bio-correspondence
08/13/01	NA (minor) [rev. #2 by S. Liu)

10. **PHARMACOLOGICAL CATEGORY:** Antifungal agent (treatment of local yeast infections)

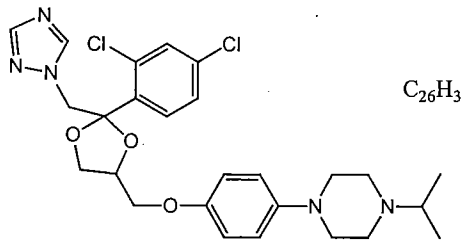
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):** N/A

13. **DOSAGE FORM**: Vaginal cream

14. **POTENCY**: 0.8%

15. **CHEMICAL NAME AND STRUCTURE:**
cis-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine.



$C_{26}H_{31}Cl_2N_5O_3$

15. **RECORDS AND REPORTS**: N/A

16. **COMMENTS**: At the conclusion of the review cycle #2, there were no remaining CMC deficiencies. Taro conducted a new (second) clinical study using a new batch of Terconazole Vaginal Cream, 08%, lot #S172-52855. This amendment is not approvable because of MINOR CMC deficiencies, related to DS specifications and typographical errors. BE review is pending.

18. **CONCLUSIONS AND RECOMMENDATIONS**: Not Approvable (MINOR).

19. **REVIEWER**: Ramnarayan S. Randad, Ph.D. **DATE COMPLETED**: 01/17/03
DATE REVISED: 01/21/03

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

38. **CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 75-953 **APPLICANT:** Taro Pharmaceuticals USA Inc.

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies

Please reinstate specification and limit for the _____ _____ in your revised drug substance specifications.

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

1. Please correct the following typographical errors:

   a. On page 3 of your cover letter you stated a limit for _____ of NMT _____.

   b. The Test Date for the 3-month test station in your accelerated condition Stability Evaluation Summary, on page 33, is November 22, 2002.

   c. In your December 3, 2002 amendment for Chemistry, Manufacturing and Controls information, the cover letter and 356h form referenced an incorrect ANDA number (75-866). In the future, please reference the correct ANDA number in your submission.

2. The bioequivalence portion of your application is under review. Deficiencies, if any, will be communicated to you under a separate cover.

3. Please submit all available room temperature stability data.

Sincerely yours,

Paul - for 12/5/03

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

cc: ANDA 75-953
Field Copy
Division File

Endorsements:

HFD-620/R. S. Randad, Ph.D./ R Randad 1/21/03
HFD-620/S. Liu, Ph.D./ S.H. Liu 1/23/03
HFD-617/W. Pamphile, Pharm. D./ WP 1/23/03

V:\firmsnz\taro\ltrs&rev\75953.REV03.NA.doc

F/T by:
Not Approvable (MINOR AMENDMENT)

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** No. 4 (Rev. #1 & 2 by S. Liu, & 3 by Randad)

2. **ANDA #** 75-953 [Terconazole Vaginal Cream, 0.8%]

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Telephone: (914) 345-9001 Ext. 298. FAX: (914) 345-8728

4. **LEGAL BASIS OF SUBMISSION:** 505(J) of the FD&C Act.

5. **SUPPLEMENT(s)/AMENDMENT(s):** 75-953/AMEND

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Terconazole Vaginal Cream, 0.8%

7. **SUPPLEMENT(s)/AMENDMENT(S) PROVIDE(s):** response to the Agencies NA Letter dated January 30, 2003.

9. **AMENDMENTS AND OTHER DATES:**

Taro:

08/31/00	Original submission
09/21/00	New Correspondence (Re: Bio issue)
09/22/00	Submission of CNC ESD
10/20/00	New correspondence (Re: bio issue)
10/26/00	New correspondence (Re: bio issue)
05/22/01	Amendment (minor)
07/03/01	Telephone amendment
07/31/01	New correspondence (Re: bio issue)
12/03/02	New correspondence (new clinical batch)
02/28/03	Amendment (minor) **(subject of this review)**
05/21/03	Amendment (labeling)
08/21/03	Amendment (bio)

FDA:

08/31/00	Date Acceptable for filing
10/04/00	Date of acknowledgment letter
02/21/01	NA (minor) [rev. #1 by S. Liu)
06/06/01	bio-correspondence
08/02/01	bio-correspondence
08/13/01	NA (minor) [rev. #2 by S. Liu)
01/30/03	NA (minor) [rev. #3 by Randad)
06/05/03	Labeling -correspondence
03/05/2004	Bio -correspondence

10. **PHARMACOLOGICAL CATEGORY**: Antifungal agent (treatment of local yeast infections)

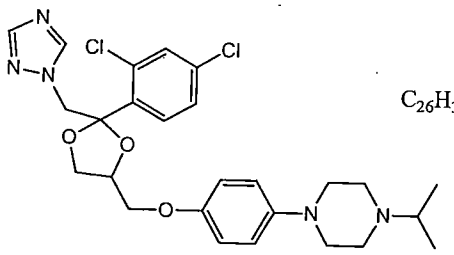
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**: N/A

13. **DOSAGE FORM**: Vaginal cream

14. **POTENCY**: 0.8%

15. **CHEMICAL NAME AND STRUCTURE:**
cis-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine.



$C_{26}H_{31}Cl_2N_5O_3$

15. **RECORDS AND REPORTS**: N/A

16. **COMMENTS**: CMC is deficient. BE and Labeling sections are satisfactory.

18. **CONCLUSIONS AND RECOMMENDATIONS**: Not approval

19. **REVIEWER**: Ramnarayan S. Randad, Ph.D.

RSRandad 3/15/04

DATE COMPLETED: 03/21/03
DATE REVISED: 03/25/03
DATE REVISED: 02/26/04
DATE REVISED: 03/08/04
DATE REVISED: 03/15/04

APPEARS THIS WAY
ON ORIGINAL

Redacted 8 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

cc: ANDA 75-953
Field Copy
Division File

Endorsements:

HFD-620/R. S. Randad, Ph.D./ RSRandad 3/15/04
HFD-620/S. Liu, Ph.D./ S.H. Liu 3/16/04
HFD-617/W. Pamphile, Pharm. D. 3/16/04

V:\firmsnz\taro\ltrs&rev\75953.CR04.NA.doc

F/T by:

Not approvable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** No. 5 (Rev. #1 & 2 by S. Liu & Rev. #3 & 4 by R. Randad)

2. **ANDA #** 75-953 [Terconazole Vaginal Cream, 0.8%]

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Telephone: (914) 345-9001 Ext. 298. FAX: (914) 345-8728

4. **LEGAL BASIS OF SUBMISSION:** 505(j) of the FD&C Act.

5. **SUPPLEMENT(s)/AMENDMENT(s):** 75-953/AMEND

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Terconazole Vaginal Cream, 0.8%

7. **SUPPLEMENT(s)/AMENDMENT(S) PROVIDE(s):** response to the Agencies NA Letter dated March 17, 2004.

9. **AMENDMENTS AND OTHER DATES:**

Taro:

08/31/00	Original submission
09/21/00	New Correspondence (Re: Bio issue)
09/22/00	Submission of CNC ESD
10/20/00	New correspondence (Re: bio issue)
10/26/00	New correspondence (Re: bio issue)
05/22/01	Amendment (minor)
07/03/01	Telephone amendment
07/31/01	New correspondence (Re: bio issue)
12/03/02	New correspondence (new clinical batch)
02/28/03	Amendment (minor)
05/21/03	Amendment (labeling)
08/21/03	Amendment (bio)
09/04/03	NC
03/22/04	Amendment (MINOR, CMC)

FDA:

08/31/00	Date Acceptable for filing
10/04/00	Date of acknowledgment letter
02/21/01	NA (minor) [rev. #1 by S. Liu)
06/06/01	bio-correspondence
08/02/01	bio-correspondence
08/13/01	NA (minor) [rev. #2 by S. Liu)
01/30/03	NA (minor) [rev. #3 by R. Randad)
06/05/03	Labeling -correspondence
03/05/04	Bio -correspondence
03/17/04	NA (minor) [rev. #4 by R. Randad)

10. **PHARMACOLOGICAL CATEGORY:** Antifungal agent (treatment of local yeast infections)

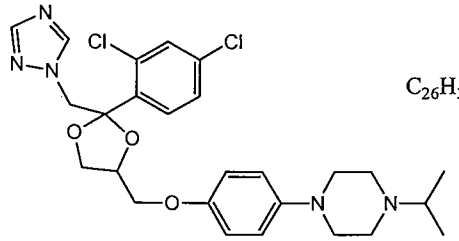
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):** N/A

13. **DOSAGE FORM:** Vaginal cream

14. **POTENCY:** 0.8%

15. **CHEMICAL NAME AND STRUCTURE:**
cis-1-[*p*-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine.



$C_{26}H_{31}Cl_2N_5O_3$

15. **RECORDS AND REPORTS:** N/A

16. **COMMENTS:** CMC, BE and Labeling sections are satisfactory.

18. **CONCLUSIONS AND RECOMMENDATIONS:** approval

19. **REVIEWER:** Ramnarayan S. Randad, Ph.D. **DATE COMPLETED:** 03/25/04

Endorsements:

HFD-620/R. S. Randad, Ph.D./ RSRandad 3/25/04
HFD-620/S. Liu, Ph.D./ Qing Liu for Shiowlin 3/24/04
HFD-617/W. Pamphile, Pharm. D./ WP 3/25/04

V:\firmsnz\taro\ltrs&rev\75953.CR05.A.doc

Redacted 8 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #5

cc: ANDA 75-953
Field Copy
Division File

Endorsements:

HFD-620/R. S. Randad, Ph.D./ 3/25/04
HFD-620/S. Liu, Ph.D./ for 3/25/04
HFD-617/W. Pamphile, Pharm. D./ 3/25/04

V:\firmsnz\taro\ltrs&rev\75953.CR05.A.doc

F/T by:

approvable

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
75-953	Ramnarayan S. Randad	March 8, 2004

DRUG PRODUCT:
Terconazole Vaginal Cream, 0.8%

FIRM:
Taro Pharmaceuticals USA, Inc.

DOSAGE FORM:	STRENGTH:
Vaginal Cream	0.8%

cGMP:
Satisfactory, February 03, 2004, J. Amrogio (HFD-322) .

BIO:
Satisfactory, March 2, 2004, reviewer C. Y. Kim

VALIDATION - *(Description of dosage form same as firm's):*
Not required.

STABILITY:
The containers in the stability studies are identical to those in the container section.

LABELING:
Acceptable, Ruby Wu, June 4, 2003.

STERILIZATION VALIDATION *(If applicable)*:
N/A

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:
[redacted]

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*:
The stability batch size of Terconazole Vaginal Cream, 0.8%, Lot# S172-52855 is [redacted]

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:
The proposed production batches are [redacted]

Signature of chemist:	Signature of supervisor:
R Randad 3/8/04	Anuja Patel 3/8/04

V:\FIRMSAM\TARO\LTRS&REV\75953APSUM.DOC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

BIOEQUIVALENCE REVIEW(S)

Review of a Bioequivalence Study with Clinical Endpoints

ANDA	**75-953**
Drug Product:	**Terconazole Vaginal Cream, 0.8%**
Sponsor:	Taro Pharmaceuticals Inc.
Reference Listed Drug:	Terazol® 3 Vaginal Cream 0.8% (Ortho McNeil Pharmaceuticals), NDA 19964 (2/21/91)
Reviewer:	Carol. Y. Kim, Pharm.D.
Submission dates:	December 3, 2002, August 21, 2003, September 4, 2003
Date of Review:	March 1, 2004

V:/firmsnz/taro/ltrs&rev/75953AB1202.mor

I. Introduction

Terconazole Vaginal Cream

Terconazole vaginal cream is indicated for the local treatment of *vulvovaginal candidiasis (moniliasis)*. Terazol® 3 Vaginal Cream is known to be effective only for vulvovaginitis caused by the genus *Candida*. The patient is instructed to apply the cream intravaginally once daily at bedtime for three consecutive days.

Vulvovaginal Candidiasis

Vulvovaginal Candidiasis (VVC), caused by *Candida albicans,* is one of the most common gynecological infections. It produces vulvar pruritus, burning, or irritation, generally without symptoms of increased vaginal discharge or malodor. Signs of vulvovaginal candidiasis include vulvar erythema, edema, fissures, and tenderness with a white scanty vaginal discharge that sometimes takes the form of white thrush like plaques or cottage cheese-like curds adhering loosely to the vaginal mucosa. The diagnosis of *vulvovaginal candidiasis* usually involves the demonstration of hyphae or pseudohyphae by microscopic examination of vaginal fluid. Microscopic examination is less sensitive than culture but correlates better with symptoms.

II. Background

- **ANDA**

8/31/00: The sponsor's original ANDA 75-953 (study #TRCZ8-9908) was submitted and filed as a potential first generic in the OGD.

5/16/01: The OGD medical officer completed the ANDA review and issued several deficiency comments and asked the sponsor to provide additional information.

7/12/01: In response to the OGD medical officer's deficiency comments, the sponsor acknowledged that their re-analysis on the evaluable population, excluding patients as

recommended by the OGD medical officer, does not demonstrate the bioequivalence of their product due to reduction of sample size.

7/18/01: The OGD medical officer further clarified and provided detailed comments related to the protocol for the future new study.

12/3/02: The sponsor modified the protocol and submitted a new study (TRCZ8R-0104) based on the Agency's recommendation. They changed the primary endpoint visit (post-treatment visit) from the previously proposed 28-42 days to 21-30 days. For early return visit, the sponsor identified two separate protocol populations, days 7-16 and days 7-10. The analyses from both populations were submitted for the review.

8/21/03: Based on this reviewer's request, the sponsor submitted additional data set including samples of Case Report Form. Since no patient was identified with a negative baseline fungal culture, this reviewer asked the sponsor to provide an explanation. Regarding the baseline screening process, the sponsor responded that only symptomatic patients identified with pseudohyphae, hyphae, or budding yeasts were cultured and enrolled into the study and patients with negative KOH smears were not enrolled.

- **NDA**

For the approval of NDA 19-964 (Terazol® Vaginal Cream) in the treatment of vulvovaginal candidiasis, R.W. Johnson Pharmaceutical Research Institute submitted 3 placebo controlled clinical studies (F85-080, F85-083, and F85-084). Two studies (F85-083, F85-084) compared Terazol® Vaginal Cream, 0.8% against their higher strength cream (1.6%) and a vehicle/placebo group. Study F85-080 included 7-day treatment of 2% miconazole vaginal cream in addition to Terazol® 0.8%, Terazol® 1.6% and a placebo.

In study F85-080, the placebo clinical and therapeutic cure rates were 31.0% and 28.2%, respectively. In two other studies, F85-083 and F85-084, the placebo clinical cure rates were 33.3% and 18.3%, respectively. Therapeutic cure rates for the placebo/vehicle from these two studies were 33.3% and 13.3%, respectively. A patient was considered a clinical cure if signs and symptoms that were present at admission were significantly improved on the second return visit and normal or eradicated on the third return visit (primary endpoint). A patient was considered a therapeutic cure if she had both a clinical cure and had both KOH and fungal culture negative.

III. Study Information

Protocol Number: TRCZ8R-0104

Title: A Bioequivalence Study of Two Terconazole 0.8% Vaginal Cream Treatments For Patients with Clinically Symptomatic and Mycologically Confirmed Vulvovaginal Candidiasis.

Objective: To establish the bioequivalence of Terconazole 0.8% vaginal cream (the test product) manufactured by Taro and Terazol 3® 0.8% vaginal cream (the reference listed drug, RLD) manufactured by Ortho Pharmaceuticals and compare the adverse event profiles of the two creams.

Study Design:

This was a randomized, double-blind, parallel-group study design comparing the two following products:

1. Test: Terconazole Vaginal Cream, 0.8%, Taro Pharmaceuticals, Inc., administered intravaginally once daily for three days
2. Reference: Terazol 3® (terconazole vaginal cream, 0.8%), Ortho-McNeil Pharmaceuticals, administered intravaginally once daily for three days

- *The following lot numbers were used in the study:*

1. *Test product: Terconazole Vaginal Cream, 0.8%, lot #(L)S172-52855*
2. *Reference Product: Terazol 3® (terconazole vaginal cream, 0.8%), lot #(L)21C563 and (L)21N445*

Reviewer's Comments: *In the past, the OGD has not required vehicle control arms for the approval of other sponsor's generic vaginal products (e.g., miconazole vaginal cream for 7 day regimen) for the indication of vulvovaginal candidiasis (VVC). The sponsor followed the general study design recommended in the CDER Draft Guidance for Industry: Vulvovaginal Candidiasis-Developing Antimicrobial Drugs for Treatment (7/98). This guidance does not recommend a vehicle/placebo arm for trials of new vaginal drug products because the vehicle itself may have an effect on the vaginal environment. However, placebo/vehicle cure rates up to 30% have been observed in previous clinical trials for the treatment of VVC. It is critical that bioequivalence studies have adequate sensitivity to show any differences in cure rates between active treatment groups. Therefore, both test and reference cure rates need to be significantly higher than 30% or the sponsor will need to provide additional information regarding spontaneous resolution of VVC to show that the study is sensitive enough to show a difference between products.*

Study Population:

Female Patients at least 18 years of age or older diagnosed with vulvovaginal candidiasis. Patients must meet the following criteria to be enrolled in the study:

Inclusion Criteria

- Female patients aged 18 years or older;
- Symptomatic vulvovaginitis. Subsequently, a positive smear (10% KOH wet mount) and a culture positive for *Candida albicans, Candida glabrata (Torulopsis glabrata), Candida parapsilosis,* or *Candida tropicalis* must be demonstrated for the patient to be considered evaluable;
- Presence of at least one of the following symptoms as assessed by the patient: itching or burning;

- Presence of at least one of the following clinical signs as assessed by the physician: vulvovaginal erythema, vulvovaginal edema, excoriation;
- Physical assessment within normal limits (excluding vulvovaginal infection) at screening. Minor variations, which are not clinically significant, were to be acceptable at the discretion of the investigator;
- Agreement to refrain from sexual activities and from using contraceptive creams, foams, or other chemical barriers during the treatment period;
- Signed informed consent after the study has been fully explained and before any procedures dictated by this protocol were performed.

Exclusion Criteria

- Pregnancy – first trimester;
- Nursing mother;
- Uncontrolled diabetes mellitus;
- Use currently or within the previous 7 days of the following medications:
    - Oral antibiotics, antifungal, or anti-trichomonal products
    - Topically applied (genital area) antibiotics, antifungals, anti-trichomonal, or anti-inflammatory products;
- Use of any investigational drug within the past 30 days;
- Use of any injectable or oral corticosteroid, immunosuppressive, or immune-stimulating drug within the past 6 months;
- Treatment for *candida* infection within the previous 3 months;
- Vulvovaginal infection other than *candida* species. This includes patients with active genital herpes, HPV, bacterial vaginosis, and patients who test positive for: *Trichomonas vaginalis, N. gonorrhea,* or *Chlamydia trachomatis;*
- Gram stain Nugent score *greater than or equal to 4;*
- History of allergy or sensitivity to Terconazole, or related compounds;
- Clinically significant liver disease;
- Failure to respond to miconazole nitrate, clotrimazole, or Nystatin for a previous candida infection;
- Any other condition which would affect the patient's ability to follow the protocol.

Removal of Patients from Therapy or Assessment

Patients could discontinue from the study for any of the following reasons:

- Patient's decision to withdraw from the study.
- Development of an intercurrent condition or complication which would affect the safety of the patient or the validity of the evaluation of the patient's clinical state to an extent considered significant by the investigator.
- Use of immunosuppressive drugs, oral antibiotics or oral antifungal agents, or any other medications, creams, or ointments to the affected areas for the 4 weeks of the study.
- Failure to comply with any aspect of the protocol.

Reviewer's Comments: *According to the medical officer's review dated November 17, 1990 (NDA#19-964, Terazol® 3 Vaginal Cream), the Agency previously approved Terconazole Vaginal Cream 0.4% and Terconazole Vaginal suppositories 80 mg for use in the second and third trimesters of pregnancy on November 28, 1988.*

Study Procedures:

Visit 1(Day 1); Screening and Treatment day

- The medical history and physical examination were completed. Patients underwent laboratory testing, and a urine pregnancy test. Vaginal secretions were obtained from the inflamed vaginal wall and the following tests were conducted: a 10% KOH wet mount, a gram stain with Nugent scoring, a wet prep for *Trichomonas vaginalis*, nucleic acid amplification of *Gonorrhea* and *Chlamydia*, and a fungal culture with quantitation and speciation. The severity of clinical signs (vulvovaginal erythema, vulvovaginal edema, excoriation, and discharge) was evaluated and recorded.

- Mycological and Clinical assessments were to be made as follows:

1) Mycological Assessment

STAT 10% potassium hydroxide (KOH) smear was to be examined microscopically for the evidence of Candida (hyphae, pseudohyphae, or budding yeasts). Mycological cultures were to be examined for Candida species and reported as rare, few, moderate, or abundant per the American Society of Microbiologists (ASM) standards. Candida culture species were reported.

2) Clinical Assessment

During the physical examination of the vulva and vagina, vulvovaginal erythema, vulvovaginal edema, excoriation, and discharge were graded on a 4-point scale. Patients assessed the severity of symptoms of itching, burning, and irritation using the same 4-point scale as follows:

Investigator's symptom evaluation	Patient's evaluation	Scale
• Vulvovaginal erythema	Itching	0=none
• Vulvovaginal edema	Burning	1=mild
• Excoriation	Irritation	2=moderate
• Discharge		3=severe

To be eligible, the patient should have total clinical assessment score of at least 2.

Reviewer's Comments: *The above mentioned draft Guidance, Vulvuovaginal Candidiasis Developing antimicrobial drugs for treatment (7/98) indicates that vaginal discharge should not be included as a criteria for enrollment for evaluation of the treatment.*

Visit 2 ***(Days 7-16); 2 weeks*** **post-treatment visit & Visit 3** ***(Days 21-30); 4 weeks post treatment visit*****; Primary Endpoint Visit**

The investigator repeated clinical assessment using the same scale proposed at Visit 1. The KOH preparation and culture sample confirming the presence and species of *Candida* were also repeated for evaluation of mycological eradication. Patients were questioned concerning possible adverse drug effects and compliance with the protocol. Women of child-bearing potential performed pregnancy test at Visit 3.

The physical examination was repeated at Visit 3 to assess any changes. If the patient required further treatment, it would be prescribed and documented at this time. Any adverse events or changes to concomitant medications were to be documented.

Reviewer's Comments: *The sponsor initially proposed Days 12 to 19 and Days 26-42 for visit 2 and visit 3 in the original protocol. Based on subsequent communication with the OGD, the sponsor modified visit 2 and 3 to days 7-10 and days 21-30. The OGD recommended these visit windows because the FDA Advisory Committee meeting of 1998 suggested such a change to improve patient compliance by simplifying the timing of return visits for vaginal antifungal studies. However, the sponsor's protocol was amended to change the visit window after the study entry and the sponsor believed that it is not appropriate to disqualify a protocol that used later revisit days when there was excellent patient compliance. Therefore, the sponsor proposed to evaluate first post-treatment visit between 7-19 days (combination of 7-10 days and 12-19 days). Since no patient returned on days 17-19, the sponsor submitted per protocol population analysis on patients who revisited between days 7-16 and 21-30 for visits 2 and 3, respectively. A separate analysis was also submitted using visit windows of 7-10 days and 21-30 days for visit 2 and 3 as suggested by the Agency.*

Evaluation of Clinical Outcome

CURE – Based on the clinical assessment of erythema, discharge, edema and excoriation, and the patient's report of symptom severity for itching, irritation, and burning at the return visits, the clinical cure is defined as:

a. At week 2 visit, a reduction in total clinical score (clinically improved); and
b. *At week 4 visit*, any sign or symptom that was a 1 or 2 at baseline should be a 0, and any sign or symptom with a baseline score of 3 (severe) should be 0 or 1.

Evaluation of Mycological Outcome

Mycological cure rate-The proportion of patients who demonstrate both a negative KOH smear and a negative mycological culture both at the 2 and 4 week visits. If a patient had

a positive KOH wet mount and/or a positive culture for *candida* at either post-treatment visit, she was recorded as a mycological failure.

Evaluation of Therapeutic (overall) Outcome

Therapeutic Cure-both clinical and mycological cure

Reviewer's Comments:

- *For visit 2 evaluation, the sponsor's proposed reduction in total clinical score was not clearly defined as to how much of reduction is considered as "clinically improved". For evaluation of clinical cure, the OGD recommends dichotomized success/failure outcomes based on the clinical response at the primary endpoint visit.*
- *Therefore, patients who are considered a clinical cure (any sign or symptom that was a 1 or 2 at baseline is 0, and any sign or symptom with a baseline score of 3 (severe) is 0 or 1) and had negative KOH and negative fungal culture at visit 3 (primary endpoint) should be considered as a therapeutic cure.*
- *All scores for vaginal discharge should be disregarded, as this sign cannot be consistently correlated with the presence or absence of VVC.*
- *The sponsor has evaluated their cure rate based on mycological cure at both visit 2 and 3. The FDA preferred endpoint for the mycological outcome is based on cure at visit 3.*

The concomitant medication and adverse events were to be completed as necessary on the CRF throughout the study.

Safety:

All reported adverse events occurring during the study, whether it was considered to be related to the treatment or not, were tabulated. Safety was assessed on all patients who were enrolled and received at least one dose of the study medication.

Statistical Plan:

Primary Endpoint

All patients who were considered evaluable were included in the primary endpoint analysis. The primary endpoint is the therapeutic cure. Secondary endpoint evaluation was to be made on both clinical and mycological cure rates.

Reviewer's Comments: *The sponsor's defined primary endpoint is a therapeutic cure for patients completing visit 2 between days 7-16 and visit 3 between days 21-30. Based on the FDA Advisory Committee meeting minutes of 1998, visit 2 is recommended and is not considered as critical for the determination of bioequivalence. Therefore, any patient who met inclusion/exclusion criteria and completed visit 3 between days 21-30 regardless of visit 2 completion dates should be included in the evaluable population for the primary analysis if*

therapeutic cure/failure data at visit 3 are available. Secondary endpoint evaluation should be performed on patients with available visit 3 (days 21-30) data for clinical and mycological cures.

Sample Size

The sample size of at least 130 female patients per treatment group was estimated based on expected cure rate of 60%.

Analysis

All statistical procedures were performed as two-tailed tests using the SAS® statistical package (version 8). Effects were considered to be statistically significant if $p<0.05$. Based on the FDA suggestion, the mycological, clinical, and therapeutic cure rates and the 90%, 95%, and 99% confidence limits for the difference in the cure rates between the two treatments were presented.

Demographic and background characteristics were summarized with descriptive statistics for the comparison of treatment groups. Categorical data were summarized by the percentage of patients in each category, while continuous data were summarized by the mean, standard deviation, and standard error.

Reviewer's Comments: *For determination of bioequivalence, the OGD recommends the 90% CI of the proportional difference in the therapeutic cure rates between the test and the reference products at visit 3 (primary endpoint) be contained within -0.20 and +0.20.*

IV. RESULTS

Study Centers: 11

Study Period: September 14, 2001 to August 20, 2002

Principal Investigator: Howard Yanofsky, MD

Site	Investigator	Address	Number of patients enrolled
1			86
2			36
3			31
4			7
5			32
6			66
7			11
8			26
9			52
10			82
11			5

Subject Enrollment:

A total of four hundred thirty-four patients (434) were randomized to receive the treatment; 211 in the test and 223 in the reference groups, respectively. Of these, 6 patients (T: 3, Ref: 3) did not return for either of two post-treatment visits. No patient was identified to have a negative mycological culture at baseline visit. The distribution of patients per treatment arm for each analysis population is shown in Table I.

TABLE I – DISTRIBUTION OF PATIENTS TO TREATMENT ARMS BY ANALYSIS POPULATION (per reviewer)

Population	Terconazole N	Terazol®-3 N	Total N
Randomized	211	223	434
Did not return for visits 2 and 3	-3	-3	-6
^Intent-to-Treat (ITT)	208	220	428
No visit 3 data	-6	-10	-16
*Nugent score>=4	-27	-34	-61
Protocol Violation	-6	-9	-15
Outside visit 3 window of 21-30 days	-18	-15	-33
^^Evaluable Population (EP)	151	152	303

^included patients who applied the cream for 3 consecutive days and completed at least 1 post-baseline visit.

*per Table 3: Exclusions for Nugent Scores >=4 on Enrollment (vol. 3.1, pp. 24-25)

^^included patients who met all of the inclusion/exclusion criteria, were positive for Candida from the fungal culture at visit 1, completed clinical assessments at visit 2 and visit 3, and received no additional vaginal or systemic anti-fungal treatments during the study period.

Reviewer's Comments

- *For the evaluation of a clinical cure/failure, the sponsor did not apply their proposed criteria for identifying patients as a clinical cure. According to the protocol, patients were to be considered as a clinical cure if all individual sign or symptom that was a 1 or 2 at baseline is 0 (absent) and any sign or symptom with a baseline score of 3 is 0 or 1 based on the clinical assessment of erythema, discharge, edema, and excoriation and the patient's report of symptom severity for itching, irritation, and burning at week 4 (visit 3). However, the sponsor identified the following patients as a clinical cure in their data set: Patient with all individual sign and symptom score, except for a vaginal discharge, is 0 (absent) or decreased from a baseline score of 3 to 1 or 0 at visit 3. For the clinical assessment of the vaginal discharge, patients were considered as a clinical cure if their vaginal discharge score is decreased to a score of 1 or below or remain unchanged from the baseline score of 1 at visit 3. If the discharge score remained the same as the baseline score of 2 at visit 3 despite of the absence of all other individual signs and symptoms, she was considered as a clinical failure.*

According to the Draft CDER Guidance for Industry: Vulvovaginal Candidiasis-Development Antimicrobial Drugs for Treatment, July 1998, the presence or absence of a vaginal discharge was not recommended as a clinical sign or symptom of infection in considering the clinical outcome. Therefore, the clinical outcome should be based on all individual sign and symptom scores excluding vaginal discharge. A patient should be considered as a clinical cure if any sign or symptom, except for vaginal discharge, with a score of 1 or 2 at entry is absent and any sign or symptom, except for vaginal discharge, with a score of 3 at entry is 0 or 1 at visit 3. All scores for vaginal discharge should be disregarded.

- *The sponsor identified five patients [112 (Test), 822 (test);220 (ref), 613 (Ref); 629 (Ref)] as a clinical failure because their vaginal discharge scores at entry remained unchanged from baseline or decreased to 1 despite the absence of all other signs and symptoms at visit 3. Since a vaginal discharge is not considered for the evaluation of the clinical outcome, they should be considered as a clinical cure.*

- *The sponsor included the following patients in the per protocol population as treatment failure despite early withdrawal from the study if they had persistent clinical signs and symptoms and required further oral or topical antifungal treatment. This reviewer agrees that they should be included in the evaluable population as treatment failure as follows:*

Site #	Patient #	Treatment
9	338	Reference
5	500	Test
6	600, 610, 635, 637	Test
7	704	Test
7	709	Reference
9	933, 967	Reference

The sponsor also identified four patients (Test: 505, Ref: 157, 180, 646) as treatment failure because these patients discontinued the study due to drug related adverse events. Since these patients experienced severe itching/burning or erythema, which could have resulted from the progression of the clinical symptoms, and were subsequently treated with other topical agents, this reviewer agrees to retain these patients in the evaluable population as failure.

However, the following patients originally included by the sponsor as treatment failure should be excluded from the evaluable population analysis due to completion of visit 3 outside visit window:

> *The sponsor declared early that patient #118 (day 16, test) is a treatment failure due to positive culture at visit 2. Since all of this patient's clinical signs and symptoms were absent except for vaginal discharge at visit 2, she should be considered as clinical cure at visit 2 and be excluded from the evaluable population.*

Since patient 138 (day 31, Ref) completed visit 3 after day 30, she should be excluded form the evaluable population. She should also be considered as clinical cure at visit 2 due to absence of all clinical signs and symptoms except for vaginal discharge.

- *The sponsor's data set (vol. 3.1, p. 581) indicated that the test for chlamydia at enrollment for patient #726 (Reference) was negative. However, it was later corrected on the case report form as a positive. Due to protocol violation, the sponsor excluded this patient from the evaluable population.*

- *Four patients were retained in the evaluable population by the sponsor although no enrollment tests for Neisseria gonorrhea or Chlamydia were available. Since their fungal cultures at enrollment were positive for candida and repeated tests for Neisseria gonorrhea or Chlamydia were negative at visit 3, this reviewer agrees to include them in the evaluable population as follows.*

  T: 970
  R: 234, 405, 640

- *Since the sponsor's original study report claims that no single patient was identified to have a baseline fungal culture negative, this reviewer asked the sponsor to provide an explanation for the screening process. The sponsor responded on August 21, 2003 that symptomatic patients with KOH test positive only were enrolled into the study. The sponsor did not provide any detailed information regarding the number of patients initially screened or identified with negative KOH smear prior to enrollment visit.*

- *Patients who missed visit 2 but completed visit 3 within days 21-30 should be included in the evaluable population if they did not violate other inclusion/exclusion criteria.*

Demographics:

Of the 434 randomized female patients, 267 (62%) were Caucasian, 47 (11%) were Black, 86 (20%) were Hispanic, and 34 (8%) were classified as "other". Baseline demographics, age, and race were similar in the two treatment groups. The mean age was 35.4 (18-73) and 35.8 (19-74) years for the test and reference products, respectively. Pregnancy status at enrollment and mean gestational age by the treatment group was tabulated by the sponsor. See Table II for the reported demographic characteristics for all randomized patients.

Table II. Demographic characteristics for all randomized patients (per sponsor)

Characteristics	Test (N=211)	Reference (N=223)
Age (years)		
Mean	35.4	35.8
Range	18-73	19-74
Race		
Caucasian	128 (61%)	139 (62%)
Black	20 (9%)	27 (12%)
Hispanic	42 (20%)	44 (20%)
Other	21 (10%)	13 (6%)
Pregnancy Status		
Patients Pregnant (N)	66 (31%)	62 (28%)
Mean gestational age in weeks (range)	23 (12.2-34)	24.1 (12.0-36)

Baseline Disease Severity:

The Sponsor tabulated the baseline clinical signs and symptoms of vulvovaginal infection for all randomized patients in Table III. The mean clinical sign and symptom score for each category were similar in two treatment groups.

Table III. Baseline clinical signs and symptom rating scores of vulvovaginal infection (Per sponsor)

	Randomized patients		
Signs and symptoms	Test (n=211)	Reference (n=223)	P=
Erythema			
Mean	1.60	1.62	
SE	0.05	0.05	0.70
Edema			
Mean	1.24	1.24	
SE	0.05	0.05	0.96
Excoriation			
Mean	0.44	0.50	
SE	0.05	0.05	0.39
Itching			
Mean	1.77	1.73	
SE	0.06	0.05	0.96
Irritation			
Mean	1.27	1.32	
SE	0.07	0.06	0.64
Burning			
Mean	1.24	1.20	
SE	0.07	0.07	0.68
Discharge			
Mean	1.80	1.81	
SE	0.05	0.05	0.93
Total*			
Mean	9.36	9.42	
SE	0.27	0.26	
Range P=	2-20	3-20	0.89

*sum of individual sign/symptom scores for each patient

Efficacy Outcomes:

Based on this reviewer's request (August 18, 2003), the sponsor submitted additional data set on September 4, 2003 including a list of patients identified as therapeutic cure or failure for each visit if data were available. Table IV shows the sponsor's efficacy outcome analysis for the evaluable population.

Table IV. Efficacy outcome by treatment group for evaluable population (per sponsor)

Number of patients	N=152		N=153		Continuity Corrected		
	Test (n)	Test (%)	Reference (n)	Reference (%)	90% CI	95% CI	99% CI
Clinical Cure Failure	 115/152 37/152	 76 24	 110/153 43/153	 72 28	 (-0.052, 0.127)	 (-0.068, 0.143)	 (-0.099, 0.174)
Mycological Eradication Persistence	 100/152 52/152	 66 34	 97/153 56/153	 63 37	 (0.073, 0.121)	 (-0.09, 0.138)	 (-0.124, 0.171)
Therapeutic Cure Failure	 88/152 64/152	 58 42	 78/153 75/153	 51 49	 **(-0.031, 0.169)**	 (-0.049, 0.187)	 (-0.084, 0.0222)

Reviewer's comment: *Based on the sponsor's statistical analysis, the study demonstrates that the 90% CI for the proportional difference in therapeutic cure rates between the test and the reference products at visit 3 (included patients completing visit 2 within days 7-16) is within(-.20, +.20) . Mycological cure was defined by the sponsor as cure at both visits 2 and 3. As previously mentioned above, the OGD's preferred endpoint is a therapeutic cure at visit 3. Regardless of the mycological outcome, she should be considered as a clinical cure if any sign or symptom (except for vaginal discharge) that was a 1 or 2 at baseline is 0 and any sign or symptom (except for vaginal discharge) with a baseline score of 3 is 0 or 1 at visit 3. A patient should be considered a mycological cure if she had negative KOH and negative fungal culture at visit 3.*

For determination of bioequivalence, the evaluable population should include any patient completing visit 3 within days 21-30 regardless of visit 2 data unless they were identified as treatment failure prior to completion visit. Because the sponsor inappropriately included or excluded some patients from the ITT/evaluable population analysis, the FDA statistician is consulted for reanalysis and verification of the sponsor's data.

Adverse Events:

No death was reported in the study. In all randomized patients, a total of 90 adverse events were reported (50 test; 40 ref). The sponsor's frequency analysis of adverse events by body system is shown below in Table V. The sponsor identified 14 patients (8/211 test; 6/223 ref) with topical treatment related adverse events.

Table V
Summary of adverse events by body system (per sponsor)

Topical treatment-related adverse events

Adverse events	Test	Reference
Itching/burning/irritation	6	3
Odor	2	0
Swelling	0	1
Rash (red dots)	0	2

Severity of non-treatment related adverse events

Adverse events	Test	Reference
Mild	34	25
Moderate	5	4
Severe	3	5

Reviewer's Comments:

The overall incidence of adverse events by severity was similar in both treatment groups. Six patients (2.8%) in the test group compared to three patients (1.3%) in the reference group experienced mild to severe itching/burning/irritation at the treatment site. Among 8 patients with non-treatment related severe adverse events, one patient [#332 (Ref)] had miscarriage on day 9 after enrollment. This patient's pregnancy test result was negative prior to enrollment. The sponsor noted that she had previous history of miscarriage.

V. Formulation

Terconazole 0.8% Vaginal Cream (Taro)

		Quantity
Ingredient	STD.	% (w/w)
Terconazole	Taro	0.8
Purified Water	USP	
Polysorbate 80	NF	
Isopropyl Myristate	NF	
Cetyl Alcohol	USP	
Stearyl Alcohol	NF	
Butylated Hydroxyanisole	NF	
Polysorbate 60	NF	
Propylene Glycol	USP	

RLD*

	Quantity
Ingredient	Mg/5 Gm
Terconazole	0.8%
Purified Water	
Polysorbate 80	
Isopropyl Myristate	
Cetyl Alcohol	
Stearyl Alcohol	
Butylated Hydroxyanisole	
Polysorbate 60	
Propylene Glycol	

*Per COMIS database

The chemistry review noted (75953.REV04.NA.doc) that the formulation has not been changed from the original submission and remains satisfactory. Regulatory Branch review indicates that all inactive ingredients are acceptable for filing. (vol. 1.1.)

Reviewer's Comment: *The test formulation is qualitatively the same as the reference product.*

VI. Review of Division of Scientific Investigation (DSI) report (1/20/04)

At the conclusion of the inspection, no Form 483 was issued to the sponsor. However, the FDA field investigator asked the OGD to verify several patients' data for post-treatment exclusionary laboratory test results. Of 7 patients identified by the FDA field investigator, five patients were already excluded from the evaluable population due to protocol violation. The remaining two patients' laboratory information was corrected and incorporated into the statistical consult request on January 23, 2004 as follows:

1) Patient #157 (Reference) had positive culture result for Chlamydia (exclusion criteria) in their source document but it was not reported. Therefore, this patient should be excluded from the evaluable population.

2) Patient #175 (Reference) was excluded from the PP population analysis by the sponsor because this patient did not have enrollment test results for N. gonorrhea and Chlamydia (exclusion criteria). Based on the DSI report, the FDA investigator was able to confirm that this patient had negative laboratory results (dated 6/21/02). Therefore, this patient should be included in the evaluable population.

The DSI also concluded that the testing facility did not maintain the sealed code because the sponsor never provided the sealed code to the clinical investigators. According to the Draft Guidance, "Handling and Retention of BA and BE Testing Samples", posted 8/20/02, the sealed code should be maintained at each testing facility.

Reviewer's Comments: *The sponsor should be provided with the following information: For a blinded study, the study sponsor and/or drug manufacturer should provide a sealed code for use by FDA. The sealed code should be maintained at each testing facility. Please refer to "Handling and Retention of BA and BE Testing Samples", posted 8/20/02 for details.*

VII. Review of the FDA Statistical Report (2/26/04)

The conclusion of the FDA statistical analysis supports the bioequivalence of the test and the reference products. The 90% CI of the therapeutic success/cure rate for the evaluable population at the primary endpoint (Visit 3, test of cure visit, days 21-30) is within -.20 and +.20. See FDA statistical review for details.

Based on this reviewer's comments above, the FDA statistician provided the summary of the equivalence test for the evaluable population as shown below, and their conclusion is as follows:

Primary Endpoint: Therapeutic success/cure rate at visit 3 (test of cure visit)

Summary of equivalence analyses

visit	Test* % cure (No. of cure /total number)	Reference* % cure (No. of cure /total number)	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
Clinical cure	76.82 (116/151)	76.32 (116/152)	(-8.16, +9.17)	Yes
Mycological cure^	70.20 (106/151)	66.45 (101/152)	(-5.65, +13.20)	Yes
Therapeutic cure	61.59 (93/151)	55.92 (85/152)	(-4.28, +15.62)	Yes

***: The rate of cure or negative culture equals the number of cure/negative divided by the total number, then multiplied by 100.**
^negative KOH and culture

VIII. Conclusion

The data presented in this ANDA 75-953 demonstrate that Taro Pharmaceuticals Inc.'s Terconazole Vaginal Cream, 0.8%, is bioequivalent to the reference listed drug, Terazol® 3 Vaginal Cream, 0.8%. The FDA statistical review confirms that the 90% CI of the proportional difference in therapeutic cure rates between the test and reference products at the test-of-cure visit (Visit 3, days 21-30) is within (-.20,+.20).

IX. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 75-953, using the primary endpoint of therapeutic cure rate at the test-of cure visit (Visit 3, days 21-30), are adequate to demonstrate bioequivalence of Taro Pharmaceuticals Inc.'s Terconazole Vaginal Cream, 0.8%, with the reference listed drug, Ortho McNeil Pharmaceuticals' Terazol® Vaginal Cream, 0.8%.

1. Please note that patients that were considered a clinical cure (any sign or symptom that was a 1 or 2 at baseline is 0 (absent), and any sign or symptom with a baseline score of 3 (severe) is 0 or 1) and had eradication of fungal culture (negative KOH and negative culture) at visit 3 (primary endpoint) were considered a therapeutic cure. All scores for vaginal discharge were disregarded, as this sign cannot be consistently correlated with the

presence or absence of *Vulvovaginal Candidiasis (VVC)*. Mycological cure was evaluated only at the test-of-cure visit (Visit 3).

2. The Division of Scientific Investigation recommends you provide a sealed code for use by FDA and maintain it at each testing facility for all future bioequivalence studies. It is your responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested. Please refer to "Handling and Retention of BA and BE Testing Samples", posted 8/20/02 for details.

Carol Y. Kim

3/1/04

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date

Dena R. Hixon (MD)

3/1/04

Dena Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Date

Dale P. Conner

3/2/04

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

Date

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-953 SPONSOR : Taro Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Terconazole Vaginal Cream, 0.8%

STRENGTH(S) : 0.8%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites in Canada

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: complete (1/21/04)	Inspection results: acceptable
First Generic _____ New facility _____ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim, Pharm. D.

INITIAL : Carol Y. Kim DATE : 2/1/04

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 3/1/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : DPC DATE : 3/2/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

STATISTICAL REVIEW(S)

ANDA 75-953
Drug Product: Terconazole Vaginal Cream, 0.8%
Sponsor: Taro Pharmaceuticals Inc.
Reference Listed Drug: Terazol® 3 Vaginal Cream 0.8% (Ortho McNeil Pharm), NDA 19964 (2/21/91)
Submission dates: December 3, 2002, August 21, 2003, and September 4, 2003
V:/firmsnz/taro/ltrs&rev/75953AB.mor1202
Reviewer: Meiyu Shen, Ph.D., QMRS/OB/CDER
Requestor: Dena Hixon, MD, Carol Kim, Pharm.D., OGD/CDER, 2/5/2004

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, **Terconazole Vaginal Cream, 0.8%**, and the reference product, Terazol® 3 Vaginal Cream 0.8% (Ortho McNeil Pharm), for the treatment of vulvovaginal candidiasis and to compare the adverse event profiles of the two creams. This statistical review addresses bioequivalence.

Remarks

The sponsor submitted SAS datasets and programs to the Electronic Document Room (EDR), CDER on September 4, 2003. The datasets contain variables collected in the Case Report Forms (CRF). The statistical analyses used information from one dataset: trcz8s.xpt.

The following adjustments to these submitted datasets were made in accordance with recommendations of FDA medical reviewers and our (medical and statistical reviewers) best judgment.[1]

Exclusion/inclusion from FDA's Per protocol (PP) populations

1) The FDA reviewers agree with the sponsor to retain the following four patients in the PP population as treatment failures: 505 in the test treatment group, 157, 180, and 646 in the reference treatment group; these patients were discontinued early due to drug related adverse events.

2) The FDA reviewers agree with the sponsor to retain the following ten patients, who withdrew early from the study despite persistent clinical signs and symptoms, in the PP population as treatment failures.

Site #	*Patient #*	*Treatment*
9	*338*	*Reference*
5	*500*	*Test*
6	*600, 610, 635, 637*	*Test*
7	*704*	*Test*
7	*709*	*Reference*
9	*933, 967*	*Reference*

[1] Please see the details in the FDA medical reviewer's report and summary table on pages 10-12.

3) Two patients (118 and 138) were excluded from the PP population by FDA reviewers due to completion of visit 3 outside visit window.
4) Patient 726 (reference) was excluded from the PP population.
5) FDA reviewers agree with the sponsor to include the following patients in the PP population: 970 in the test treatment and 234, 405, 640 in the reference treatment

Re-evaluation/revision of clinical, mycological, therapeutic response at visit 3

1) *FDA medical reviewer's comments: According to the Draft CDER Guidance for Industry: Vulvovaginal Candidiasis-Developing Antimicrobial Drugs for Treatment, July 1998, the presence or absence of a vaginal discharge was not recommended as a clinical sign or symptom of infection in considering the clinical outcome. Therefore, the clinical outcome should be based on all individual sign and symptom scores excluding a vaginal discharge. A patient should be considered as a clinical cure if any sign or symptom, except for a vaginal discharge, with a score of 1 or 2 at entry is absent and any sign or symptom, except for a vaginal discharge, with a score of 3 at entry is 0 or 1 at visit 3. All scores for vaginal discharge should be disregarded.*

Based on the above definition, the following patients' clinical outcome should be changed from clinical failure to clinical cure

Treatment	Patient number
Test	112, 822,
Reference	220, 613, 629, 802, 810

2) *In addition, the sponsor has evaluated their cure rate based on mycological cure at both visit 2 and 3. The FDA preferred endpoint for the mycological outcome is based on cure at visit3.*

The statistical reviewers identified the following patients whose mycological outcome should be changed from failure to cure: 613, 629, 132, 541, 544, 712, 814, 912, 928, and 1015.

3) The statistical reviewers identified the following patients whose therapeutic outcome should be changed from failure to cure: 132, 541, 544, 712, 802, 810, 912, 928, 1015, 613, 629, and 220.

Study Design

This was a multi-center, 2 arm parallel, investigator-blind study, with no placebo/vehicle – control arm, of vulvovaginal candidiasis patients who had been diagnosed by clinical examination and confirmed by KOH smear and were culture positive for candida.

A total of 434 patients were enrolled and randomly assigned to the two treatment groups in the study. There were three visits: Visit 1 – Screening and Treatment visit (Day 1), the samples for KOH wet mount and candida culture were collected. The severity of clinical signs and symptoms (vulvar/vaginal itching, burning, irritation, edema, erythema/excoriation, and discharge) was evaluated by using a score (0-3, none-severe). The patient was eligible for the study who had presence of vulvovaginal candidiasis infection confirmed by positive KOH smear and moderate signs and symptoms score (at least 2 signs/symptoms with a minimum score of 2). Each eligible patient was instructed

to apply the study cream into vagina once a day at bedtime for 3 consecutive days, starting at Day 1. Visit 2 – 2 weeks post-treatment visit was performed on from Day 7 to Day 16 [a separate analysis was also done using days 7-10] Visit 3 - Test of Cure visit (Days 21-30), the mycological evaluation (KOH and culture) and clinical evaluation (signs and symptoms) were performed.

Outcome Variables at Visit 3

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

The criteria were based on the FDA's current evaluability criteria as described in the draft Guidance, Vulvovaginal Candidiasis - Developing Antimicrobial Drugs for Treatment (7/98).

Clinical Cure is established when any sign or symptom that was a 1 or 2 at baseline is 0, and any sign or symptom with a baseline score of 3 (severe) is 0 or 1. All scores for vaginal discharge should be disregarded, as this sign cannot be consistently correlated with the presence or absence of VVC.
Mycological Cure means a negative culture (no growth) for candida.
Therapeutic Cure is defined as both clinical and mycological cures.

Statistical Analysis Methods

Equivalence Analysis
Based on the usual method used in the Office of Generic Drugs (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

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

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

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

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

We reject H_0 if $L \geq -.20$ and $U \leq .20$

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

Analysis Populations

Per Protocol population (PP) – All subjects who completed the study and were evaluable for the analyses based on the protocol and the FDA medical reviewer's best judgment. According to the FDA medical reviewers, the determination of clinical equivalence of the two active treatments was to be assessed using the Per Protocol population (PP).

Statistical Analysis Results

A total of 434 patients were enrolled. The FDA's PP population included 303 patients.

Table 1– Distribution of patients to treatment arms in the Per protocol population (per medical reviewer)

Population	Terconazole N	Terazol®-3 N	Total N
Randomized	211	223	434
Did not return for visits 2 and 3	-3	-3	-6
^Intent-to-Treat (ITT)	208	220	428
No visit 3 data	-6	-10	-16
*Nugent score>=4	-27	-34	-61
Protocol Violation	-6	-9	-15
Outside visit 3 window of 21-30 days	-18	-15	-33
^^Per Protocol Population (PP)	151	152	303

^included patients who applied the cream for 3 consecutive days and completed at least 1 post-baseline visit.
*per Table 3: Exclusions for Nugent Scores >=4 on Enrollment (vol. 3.1, pp. 24-25)
^^included patients who met all of the inclusion/exclusion criteria, were positive for Candida from the fungal culture at visit 1, completed clinical assessments at visit 2 and visit 3, and received no additional vaginal or systemic anti-fungal treatments during the study period.

Demographics and baseline

Of the 434 randomized female patients, 267 (62%) were Caucasian, 47 (11%) were Black, 86 (20%) were Hispanic, and 34 (8%) were classified as "other". Baseline demographics, age, and race were similar in two treatment groups. The mean age was 35.4 (18-73) and 35.8 (19-74) years for the test and reference products, respectively. Pregnancy status at enrollment and mean number of weeks pregnant by treatment group was tabulated by the sponsor. There was no significant difference in these demographic characteristics between the two treatment arms.

Table 2. Demographic characteristics for all randomized patients (per sponsor)

Characteristics	Test (N=211)	Reference (N=223)
Age (years)		
Mean	35.4	35.8
Range	18-73	19-74
Race		
Caucasian	128 (61%)	139 (62%)
Black	20 (9%)	27 (12%)
Hispanic	42 (20%)	44 (20%)
Other	21 (10%)	13 (6%)
Pregnancy Status		
Patients Pregnant (N)	66 (31%)	62 (28%)
Mean Number of Weeks Pregnant (range)	23 (12.2-34)	24.1 (12.0-36)

An analysis of the frequencies and chi-square tests for homogeneity of signs/symptoms for the PP populations at the enrollment visit was performed. There was no significant difference between treatment arms for any of the signs/symptoms.

Equivalence Analyses

We carried out equivalence analyses for the clinical cure rate, mycological cure rate, and therapeutic cure rate using the FDA's PP population at visit 3 only (test of cure visit).

Table 3 Summary of equivalence analyses

visit	Test* % cure (No. of cure /total number)	Reference* % cure (No. of cure /total number)	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
Clinical cure	76.82 (116/151)	76.32 (116/152)	(-8.16, +9.17)	Yes
Mycological cure	70.20 (106/151)	66.45 (101/152)	(-5.65, +13.20)	Yes
Therapeutic cure	61.59 (93/151)	55.92 (85/152)	(-4.28, +15.62)	Yes

*: The rate of cure or negative culture equals the number of cure/negative divided by the total number, then multiplied by 100.

The equivalence test was passed for the FDA's PP population for the clinical, mycological, and therapeutic cure rates at visit 3.

Comments on the Sponsor's Analysis

The Sponsor's results were obtained using the sponsor's PP population and endpoints without adjustment (see Remarks, page 1-2 of this review). The differences between our results and the Sponsor's results were caused in part by the changes to the datasets in accordance with recommendations of the OGD medical reviewer and our (medical and statistical reviewers) best judgment. Another possible source of difference was the use of 95% rather than 90% confidence intervals.

Table 4 summarizes the results from the sponsor's report.

Table 4 Summary of equivalence analysis (Per sponsor)

Visit 3	Test % cure (No. of cure /total number)	Reference % cure (No. of cure /total number)	95% Confidence interval for Test vs. Ref. (%)	95% CI is within (-20%, 20%)	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
Clinical cure	75.66 (115/152)	71.89(110/153)	(-6.8, 14.3)	Yes	(-5.20, 12.7)	Yes
Mycological cure	65.79(100/152)	63.40 (97/153)	(-9.00,13.8)	Yes	(-7.3, 12.1)	Yes
Therapeutic cure	57.89 (88/152)	50.98 (78/153)	(-4.9, 18.7)	Yes	(-3.1, 16.9)	Yes

Safety

Please see the details in the OGD medical reviewer's report.

Conclusion

The equivalence test was passed for clinical, mycological, and therapeutic cure rates for the FDA's Per Protocol (PP) population at visit 3 (test of cure visit).

2/26/04

Meiyu Shen, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 2/26/04

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado 2/26/04

Stella G. Machado, Ph.D.
Director, QMR
cc:
HFD-600 Dena R Hixon, Carol Y Kim
HFD-705 Stella G. Machado, Donald J. Schuirmann, Meiyu Shen
HFD-705 QMR Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : September 8, 2000

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 9/8/00

SUBJECT: Examination of the request for a clinical study submitted with an ANDA for Terconazole Vaginal Cream, 0.8% to determine if the application is substantially complete for filing.

Taro Pharmaceuticals, U.S.A. Inc. has submitted ANDA 75-953 for Terconazole Vaginal Cream, 0.8%. The ANDA contains a first generic. In order to accept anf ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for clinical study submitted by Taro on August 31, 2000 for its Terconazole product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

__X__ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

_____ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

— INCOMPLETE

9/20/00

Dr. FANNING SHOULD BE CONSULTED

Director, Division of Bioequivalence

9/26/00
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 75-953 DRUG NAME Terconazole Vaginal Cream, 0.8% FIRM Taro Pharm. USA, Inc.

DOSAGE FORM(s) Topical Cream

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol (Clinical)	✓		2 or 3-Leg Parallel Design	2-Leg Parallel	170 Patients recruited. Two-Treatment Parallel Design.
Assay Methodology		X			N/A
Procedure SOP		X			N/A
Methods Validation		X			N/A
Study Results Ln/Lin		X			N/A
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data		X			Not Applicable.
Pre-screening of patients	✓				
Chromatograms		X			Not Applicable
Consent forms	✓				
Composition	✓				
Summary of study	✓				
Individual Data & Graphs, ~~Linear &~~ Ln	✓	X N/A			
PK/PD data disk		X			Not applicable
Randomization Schedule	✓				
Protocol Deviations	✓				
Financial Disclosure	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site		X			N/A
Study investigators	✓				
Medical Records	~~X~~	✓			need
Clinical Raw Data	✓				
Test Article Inventory		X			
BIO Batch Size	[ ]				
Assay of active content drug	✓		Test + Ref.	Test	Ref. Lot Assay is needed.
Content uniformity	✓		Test + Ref.	Test	Ref. Lot C. Unif. is needed.
Date of manufacture	✓				
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	N/A				

Additional comments:

① - Patients observed @ enrollment, 2 wks, 4 wks provided.

② - CVs of Investigators provided.

③ - Potency and content uniformity data on reference drug should be provided.

④ - Test article inventory records should be provided.

⑤ - Dr. Mary Fanning should be consulted for additional comment.

Recommendation: ~~COMPLETE~~ / INCOMPLETE

See comments # 3-5.

Reviewed by

CONCUR: 9/20/00

Date 9/19/00

Revised 6/7/2000

APPEARS THIS WAY
ON ORIGINAL

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-953 Applicant **Taro Pharmaceuticals U.S.A., Inc.**

Drug **Terconazole Vaginal Cream** Strength(s) 0.8 %

APPROVAL ■ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 2/25/04 Initials MS	Date 4/6/04 for Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)

Determ. of Involvement? Yes ☐ No ☒

Pediatric Exclusivity System

RLD = NDA# 19-964

Patent/Exclusivity Certification: Yes ☑ No ☐

Date Checked 4/6/04

If Para. IV Certification- did applicant Nothing Submitted ☒

Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐

Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐

Has case been settled: Yes ☐ No ☐ Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

Type of Letter:

Comments:

No patents/exclusivities ∴ FA

2. Project Manager, **Wanda Pamphile** Team 5 Review Support Branch	Date 2-24-04 Initials WP	Date 3/29/04 Initials

Original Rec'd date 8-31-00

Date Acceptable for Filing 8-31-00 ✓

Patent Certification (type) I

Date Patent/Exclus.expires N/A

EER Status Pending ☐ Acceptable ■ OAI ☐

Date of EER Status 2/3/04

Date of Office Bio Review 3-2-04

Date of Labeling Approv. Sum 6-5-03

Citizens' Petition/Legal Case Yes ☐ No ☐ Date of Sterility Assur. App. N/A

(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ■

First Generic Yes ■ No ☐ MV Commitment Rcd. from Firm Yes ■ No ☐

Acceptable Bio reviews tabbed Yes ☐ No ■ Modified-release dosage form: Yes ☐ No ■

Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☐ Date

Previously reviewed and CGMP def./NA Minor issued ☐ Date

Comments:

3. ~~Div. Dir./Deputy Dir.~~ Chemistry ~~Div. I or II~~ Comments:		Date 3/29/04 Initials DEC.

The CMC section is satisfactory. Forwarded for FGAA

4. Frank Holcombe **First Generics Only** Assoc. Dir. For Chemistry Comments: (First generic drug review)	For Frank	Date 4/5/04 Initials

CMC OK

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date _____
Initials _____

RLD= Terazol 3 Vaginal Cream, 0.8%
Ortho McNeil Pharmaceutical, Inc. NDA 19-964 (001)
There are no unexpired patents or exclusivity listed in the current Orange Book for this drug product.

6. Peter Rickman
Director, DLPS
Date 4/6/04 (Faxed for)
Initials _____
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable ES's dated 3/3/04 (Received 4/6/04). No O.N.F. alerts noted. Bioequivalence study with clinical endpoints found acceptable 3/2/04. Statistical analysis also found acceptable. DSI site investigations reviewed and found acceptable. Office-level bio endorsed 3/2/04. FPL found acceptable for approval 6/5/03, as updated 2/26/04. CMC found acceptable for approval 3/2/04. Methods validation not requested for this ANDA - same methods as for ANDA's for ANDA 76-043 for Terconazole. First-generic CMC review has also been completed.

6. Robert L. West
Deputy Director, OGD
Date 4/6/2004
Initials (Robert West)
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments:

This ANDA is recommended for approval.

7. Gary Buehler
Director, OGD
Date 4/6/04
Initials GB
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team **Wanda Pamphile**
Review Support Branch 5
Date 4/6/04
Initials CL
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
11:15 Time notified of approval by phone 1:20 Time approval letter faxed
FDA Notification:
4/6/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/6/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

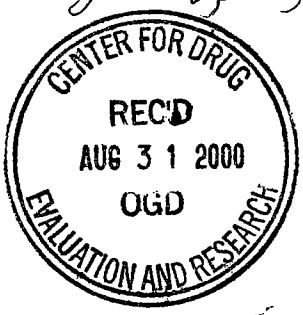
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-953

CORRESPONDENCE

Check for filing
S. Middleton 9/25/00
505(b)(2)



August 31, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA for Terconazole Vaginal Cream, 0.8%**
This application will include a CMC electronic submission.

Dear Mr. Sporn:

Taro Pharmaceuticals USA Inc. submits today an original Abbreviated New Drug Application (ANDA) seeking approval to market Terconazole Vaginal Cream, 0.8% that is bioequivalent to the listed drug, Terazol® 3, manufactured by Ortho Pharmaceutical Corporation pursuant to NDA 19-964.

This ANDA consists of four volumes. Taro Pharmaceuticals USA Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange folders. The diskette with the biostudy data is included in the archival copy, section VI "Bioavailability and Bioequivalence".

This application will also include the CMC Electronic Submission in New Correspondence within 30 days of this submission.

Taro Pharmaceuticals USA Inc. hereby certifies that, the field copy of this ANDA submission contained in burgundy folders is a true copy of the technical sections of the ANDA. The field copy also contains a copy of the signed 356h form and a certification that the contents are a true copy of the technical sections of the ANDA.

If there are any questions regarding this application, or if additional information is required, please contact us at:

Taro Pharmaceuticals USA, Inc.,
Attn: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

Sincerely,
Taro Pharmaceuticals Inc.

Derek Ganes, Ph.D.
V.P. , Regulatory Affairs

/Vesna Lucic

Enclosures:

Archival Copy (1 set):
All Sections (I - XX), 4 volumes (Blue)
Review Copies:CMC (Sections I-V and VII-XX), 2 volumes (Red)
Bioequivalence (Sections I-VII): 2 volumes (Orange)
Field Copy (1 set)
CMC (Sections I-V and VII-XX), 2 volumes (Burgundy)

Taro Pharmaceuticals Inc.

September 22, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-953:Terconazole Vaginal Cream, 0.8%
New Correspondance
This correspondance includes a CMC ESD electronic submission

Dear Mr. Buehler,

Reference is made to Taro Pharmaceuticals USA Inc.'s original Abbreviated New Drug Application (ANDA) for Terconazole Vaginal Cream, 0.8% submitted on August 31, 2000, wherein we advised the agency that a CMC ESD electronic submission would be filed within 30 days.

This correspondence includes the CMC ESD electronic submission. The electronic files have been provided in duplicate on 3.5" virus-free diskettes. The information provided in these files is identical to the hard copy ANDA submission filed on August 31, 2000. A copy of the original application cover letter has also been included.

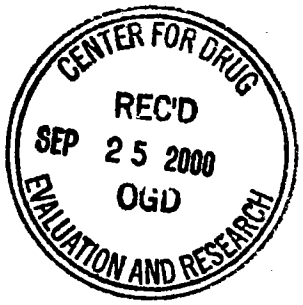
If there are any questions regarding this application, or if additional information is required, please contact:

Taro Pharmaceuticals USA, Inc.,
Attn: Kalpana Rao
Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001
Fax: (914) 345-8728

Sincerely,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/J. Hobbs, B.Sc.



130 East Drive, Bramalea, Ontario L6T 1C3 Tel: 905-791-8276 1-800-268-1975 Fax: 905-791-4473 www.taro.ca

ANDA 75-953

Taro Pharmaceuticals U.S.A., Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532

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 the telephone conversation dated September 21, 2000 and your amendment dated September 21, 2000.

NAME OF DRUG: Terconazole Vaginal Cream, 0.8%

DATE OF APPLICATION: August 31, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 31, 2000

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

In the interim, please submit the following bioequivalence data:

1. Potency and content uniformity data of reference drug
2. Test article inventory records

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

APPEARS THIS WAY
ON ORIGINAL

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5849

Sincerely yours,

Nasser Mahmud for

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

ANDA 75-953
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 _____ date 10/3/00
HFD-615/Smiddleton, CSO S. Middleton date 9/28/00
Word File
V:\FIRMSNZ\TARO\LTRS&REV\75953.ACK
F/T mjl/9/28/00
ANDA Acknowledgment Letter!

October 20, 2000

TARO

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

NEW CORRESP
NC

NAI
Elaine Th
10/25/00

RE: **ANDA 75-953**
Terconazole Vaginal Cream, 0.8%
General Correspondence

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on August 31, 2000, pursuant to 21 CFR 314.70. and your Letter received October 6, 2000, in which you requested the following information:

1. **Potency and content uniformity data on the reference drug**

   The Certificate of Analysis, indicating the potency value, for (L) 29L466 of the reference product Terazol® 3, used in the clinical study, is provided in the **supplementary page 3**. Please note that the content uniformity testing was not performed on the reference product.

2. **Test article inventory records**

   Inventory Record for test and reference product used in the Clinical Study TRCZ89908 is presented in **supplementary page 4.**

If there are any questions with regards to this information, please do not hesitate to contact us at:

Taro Pharmaceuticals U.S.A. Inc.
Kalpana Rao
Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 23 2000
OGD

Two copies of this letter are being submitted.

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ V.Lucic
cc. Acting Director, FDA, Office of International Programs

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

FEB 21 2001

ANDA 75-953

FICE OF GENERIC DRUGS, CDER, FDA
ocument Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Taro Pharmaceuticals, U.S.A. Inc. TEL: (914) 345-9001

ATTN: Kalpana Rao FAX: (914) 345-8728

FROM: Elaine Hu PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (15 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CHEMISTRY AND LABELING COMMENTS PROVIDED. BIOEQUIVALENCE PORTION IS STILL UNDER REVIEW. COMMENTS, IF ANY, WILL BE COMMUNICATED TO YOU UNDER SEPARATE COVER.

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

2/21/2001 FDA FAX (CHEMISTRY DEFICIENCIES)

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

ANDA Number: 75-953 Date of Submission: August 31, 2000

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Terconazole Vaginal Cream, 0.8%

Labeling Deficiencies:

1. CONTAINER (20 g) – Satisfactory in draft

2. CARTON (20 g) – Satisfactory in draft

3. INSERT

   a. CLINICAL PHARMACOLOGY – Revise this section to be in accord with approved labeling for this product (Terazol 3 Vaginal Cream – The R.W. Johnson Pharmaceutical Research Institute; approved July 28, 1997) that is attached.

   b. PRECAUTIONS (Pregnancy: Teratogenic Effects) – Revise this subsection to be in accord with the approved labeling for this product that is attached.

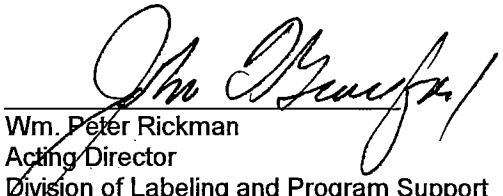
4. PATIENT INSTRUCTION SHEET (Cleaning the applicator) – Include a drawing of the separated applicator.

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.



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

Attachment: Terazol Labeling

Copy of Reference Listed Drug labeling removed.
(12 pages)

ARCHIVE COPY

TARO

Taro Pharmaceuticals Inc.

May 22, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

ORIG AMENDMENT

N/AM FPL

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 24 2001
OGD

RE: ANDA: 75-953 - Minor Amendment
Terconazole Vaginal Cream, 0.8%

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product submitted August 31, 2000. Reference is also made to the MINOR deficiencies presented in the agency's correspondence of February 21, 2001. The agency's comments have been restated in bold and are followed by Taro's response.

Chemistry

A. Deficiencies

1. Drug Master File No. ——— deficient. The holder of the DMF, ——— has been notified of the DMF deficiencies. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

Taro has been notified that the DMF holder ——— has submitted a response to their deficiency letter on March 29, 2001. This notification is provided in Attachment 1.

2. [redacted]

130 East Drive, Bramalea, Ontario L6T 1C3 Tel: 905-791-8276 1-800-268-1975 Fax: 905-791-4473 www.taro.ca

5/30/01

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

5/22/2001 TARO LETTER

Taro Pharmaceuticals U.S.A. Inc.
ATT. Kalpana Rao
Vice President, Regulatory Affairs USA
5 Skyline Drive,
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

Kalpana Rao
Vice President, Regulatory Affairs USA
/jh

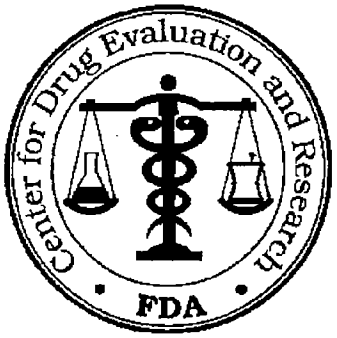
APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

ANDA 75-953

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN - 6 2001



TO: APPLICANT: Taro Pharmaceuticals, U.S.A. Inc. TEL: 914-345-9001

ATTN: Kalpana Rao FAX: 914-345-8728

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 31, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

JUN - 6 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: # 75-953 APPLICANT: Taro Pharmaceuticals

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The study report lists the following signs of vulvovaginal candidiasis (vulvovaginal erythema, edema or excoriation, and discharge) and gives a four point scale for their evaluation: 0=none; 1=mild; 2=moderrate; 3=severe. No explanation was given for these changes. You should provide an explanation for why the clinical signs and the scale for scoring them was changed and when this change occurred in relation to the study dates.

2. The study report includes itching, burning and irritation as the symptoms for evaluation and gives a four point scale 0=none, 1=mild, 2=moderate, and 3=severe. No explanation was given for these changes. You should provide an explanation for why the symptom rating scales were changed and when this change occurred in relation to the study dates.

3. No week 2 or week 4 study visit window was defined in the protocol. The protocol made no provisions for evaluation of concomitant medication use or compliance. The study report stipulates that patients were interviewed regarding the occurrence of adverse events and concomitant illnesses. You should provide the definitions for visit windows and for compliance and the patient line listings with the dates of each visit as well as the study day for each visit and a list of patients who were outside the study windows.

4. You did not provide a listing of the number of subjects enrolled at each study site. This information should be provided and an analysis of treatment by center differences in outcome should be conducted.

5. The study report modified the definition of Clinical Cure as follows: Patient had a total symptom score of 0 (discharge was allowed to be a 1) at visit 3. You should specify why the definition for Clinical Cure was changed and when this change occurred in relation to the study dates.

The usual definition of Clinical Cure includes data from both visit 2 and visit 3. At visit 2, clinical signs and symptoms should have improved. At visit 3, any sign or symptom that was a 1 or 2 at baseline the score should be 0, and any sign or symptom with a baseline score of 3(severe) should be 0 or 1.

6. Both post-treatment visits should be used for the determination of efficacy. Patients should have a Mycologic Cure at each visit and a Clinical Cure as defined in item #5.

7. The study report should define an Intent-to-Treat population. The Evaluable (or Per Protocol) population should then be defined. If patients were considered failures at visit 2, they should be included in the Evaluable population even if visit 3 data was not available. In this type of study, excluded patients are generally not replaced. Usually, enrollment is higher than the projected sample size for the Evaluable population to ensure that an adequate sample is available for final analysis.

8. Patient #117 did not have a visit 3 fungal culture and KOH and was excluded as a "Lab error". This patient was a failure at visit 2 and should be included in the final analysis as a therapeutic failure. Patient #710 was excluded because, purportedly, an interdicted organism was reported from the fungal culture. The patient listings report that this patient's fungal culture grew Candida albicans. This patient had a clinical failure at visit 2 and should be included in the final analysis as a failure. The intercurrent condition experienced by patient #303 was not specified in the study report or the line listings.

9. Only 2 among those excluded had a negative baseline fungal culture. This is an unusually low rate. Generally, all of the women who have a positive KOH smear at the baseline visit are enrolled and receive treatment, pending the results of their fungal culture that is also taken at the baseline visit. However, their study eligibility is partly determined by the results of the baseline culture, which is not available at the time of enrollment. Once the results of the fungal culture are available, those with a negative culture are identified as ineligible. Their data should be included in the Safety population. The usual rate of negative cultures with a positive KOH is approximately 20 to 30%.

You should provide information about their screening process, the timing of enrollment related to the receipt of a positive fungal culture and why their negative culture rate is so low.

10. The following patients were ineligible because they did not meet the inclusion criterion "Presence of at least one of the following symptoms as assessed by the patient: itching or burning": # 100, 102, 106, 110, 809, 811, 814, 817, 1012, and 1024. They should be excluded from the Evaluable population.

11. The following patients were ineligible because they did not meet the exclusion criterion "Gram stain Nugent score 4 or higher, or diagnosis of bacterial vaginosis": #127, 605, 715, 716, 718, 724, 801, 1007, 1009, 1017, and 1024. They should be excluded from the Evaluable population.

12. Subject #609 had no data for visit 2 and 3 but she is not counted among the exclusions. This subject is included in the Evaluable data set as a Failure. You should explain why there is no visit 2 or 3 data for this subject and why they are included in the Evaluable population as a failure.

13. Patients # 308 and 1030 do not meet the inclusion criteria that stipulate that subjects must be 18 years of age or older. They should be excluded from the Evaluable population.

14. You should provide a number of case report forms. These have not been received to date. You should provide all the patient case report forms.

Sincerely yours,

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

DATE: 6/28/01

TO: Taro Pharmaceuticals

FROM Tim Ames

PHONE: 914 - 345 - 9001

PHONE: 301-827-5765

FAX: 914 - 593 - 0078

FAX: 301 - 594 - 0180

TOTAL NUMBER OF PAGES: 2
(EXCLUDING COVER SHEET)

SPECIAL INSTRUCTIONS: Re: 75-953 & 76-043

Please respond as Telephone Amendments.

Thanks

Telephone Conversation Memorandum

ANDA: 75-953, (0.8%)
76-043, (0.4%)

DRUG: Terconazole Vaginal Cream

FIRM: Taro Pharmaceuticals USA, Inc.

PERSONS INVOLVED: Susanne, TARO
Tim Ames, FDA

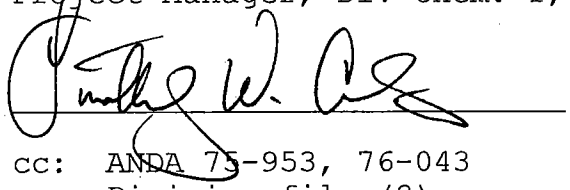
PHONE NUMBER: 914-345-9001

DATE: June 28, 2001

The follow telephone amendment deficiencies were communicated to the applicant with a request to respond as a telephone deficiency:

1. The [redacted] Testing should be included in the stability specifications as a routine test rather than as a test to be performed for the first validation batch.
2. Please separate the [redacted] you are not required to include them in the specifications.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem. I, Team 1, OGD



cc: ANDA 75-953, 76-043
Division file (2)

File: V: \FIRMSNZ\TARO\TELECONS\75953tc1.doc

Taro Pharmaceuticals Inc.

July 3, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

ORIG AMENDMENT

RE: ANDA: 75-953 - Telephone Amendment
Terconazole Vaginal Cream, 0.8%

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product submitted August 31, 2000. Reference is also made to the deficiencies presented in the agency's fax correspondence of June 28, 2001. The agency's comments have been restated in bold and are followed by Taro's response.

The deficiencies presented below represent TELEPHONE deficiencies.

1. The ——— Testing should be included in the stability specifications as a routine test rather than as a test to be performed for the first validation batch.

In a telephone conversation on April 3, 2001, between Kalpana Rao of Taro Pharmaceuticals U.S.A. Inc. and Paul Schwartz, Shing Liu, and Elaine Hue of the FDA, clarification was requested regarding the FDA's expectations for ——— Testing in connection with Taro's ANDA 76-005 for Econazole Nitrate Cream, 1%.

During that conversation Taro was advised that one iteration of ——— Testing was sufficient and that it was acceptable to perform this test on one validation batch.

Also, considering that the ——— test typically takes up to ——— from the time that the sample is drawn to the time when a full report is available, the test should be performed a

———.

At this time, Taro wishes to follow FDA's original recommendation to perform

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 05 2001
OGD

130 East Drive, Bramalea, Ontario L6T 1C3 Tel: 905-791-8276 1-800-268-1975 Fax: 905-791-4473 www.taro.ca

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

7/3/2001 TARO LETTER

ANDA 75.953

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 75-953

Food and Drug Administration
Rockville MD 20857

Taro Pharmaceuticals Inc.
Attention: Kalpana Rao
Five Skyline Drive
Hawthorne, NY 10532

JUL 25 2001

Reference Number: OGD 01-376

Dear Ms. Rao:

This letter is in response to your correspondence dated July 12, 2001. You request a meeting with the Office of Generic Drugs (OGD) to discuss the Agency's deficiency letter dated June 6, 2001 regarding ANDA 75-953, Terconazole Vaginal Cream, 0.8%. The OGD has determined that a meeting is not necessary at this time and provides the following clarification to the comments in our June 6, 2001 letter:

- Comments 1 and 2 point out instances where your protocol and the final study report differ. You did not provide an explanation for the discrepancies between the protocol and study report definitions and scoring scale. The protocol listed the clinical signs as vulvar erythema, vulvar edema, vulvar excoriation, vaginal erythema, vaginal edema, and vaginal discharge rated using a 5-point scale. However, the study report listed the clinical signs evaluated as vulvovaginal erythema, edema or excoriation, and discharge and rated them using a 4-point scale. The protocol listed the symptoms as itching and burning and rated them using a 5-point scale; whereas, the study report listed the symptoms as itching, burning, and irritation and rated them using a 4-point scale. You should have explained these changes and defined their temporal relation to the study (whether they were made before the study started or after it started). Post-hoc changes in clinical criteria and endpoints (see comment #5) are generally not encouraged.

- Comment 3 – Visit windows are generally required for this type of study since late or early visits may influence the outcome. Taking all three treatments is generally considered compliant in a three-day study. Patients who were non-compliant or had a study visit outside of the visit window are excluded from the evaluable population.

- Comment 4 – You should provide a listing of the study sites and the number of patients enrolled at each site with the study report. In addition, the statistical analysis should include an analysis of treatment-by-center effect.

- Comment 5 – An Intent-to-Treat population is generally the group of eligible patients who took at least one dose of the study drug and had at least one post-baseline visit. The evaluable population excludes patients who did not have data

for both study visits, were not compliant with their medication, or did not return during the visit window. You may consider other exclusions for this group.

- Comment 9 – In most VVC studies, approximately 20 to 30% of patients enrolled with a positive KOH are not eligible for the study because their fungal culture is negative or they have evidence of either bacterial vaginosis or trichomonas infection. In your study, only 2 of 170 (1.2%) enrolled patients had a negative fungal culture. Please explain your low rate of negative fungal culture and positive KOH.

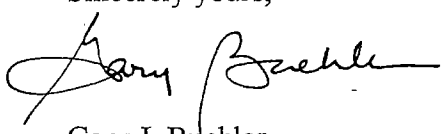
- Comment 11 – The exclusion criteria listed "Gram stain Nugent score of 4 or higher or, diagnosis of bacterial vaginosis" as an exclusion criterion. The patients listed in this comment were found to either have a gram stain Nugent score of 4 or higher or a diagnosis of bacterial vaginosis and should have been excluded from the study as protocol violations/ineligible.

- You may submit a study protocol to the Agency for review.

- Please refer to the following two guidance documents for assistance in designing a new study for this drug product: The 1990 *Draft Guidance for the Performance of a Bioequivalence Study for Vaginal Antifungal Products* and the *Draft Guidance for Industry: Developing Antimicrobial Drugs for the Treatment of Vulvovaginal Candidiasis (VVC)*. The latter guidance is intended for the development of new drug products, but contains relevant information on selection criteria, study visits, and endpoints, which are applicable to a bioequivalence study with clinical endpoints for antifungal drug products.

If you have any questions, please call Steven Mazzella, R.Ph., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,



Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

7/19/01

CC: OGD # ~~75-953~~ 01-376
Cecelia Parise, HFD-600
Robert West, HFD-611
Lizzie Sanchez, HFD-650
Mary Fanning, HFD-600
Rabi Patnaik, HFD-650
ANDA 75-953

7/24/01

Drafted by S. Mazzella
V:\~~firmsnz\taro\controls\75-953~~
firms NZ\taro\letters rev\75-953.doc

APPEARS THIS WAY
ON ORIGINAL

Taro Pharmaceuticals U.S.A., Inc.

BIOAVAILABILITY
ORIG AMENDMENT
N/AB

July 31, 2001

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

Attention: **Office of International Program**
RE: **ANDA # 75-953**
Terconazole Vaginal Cream, 0.8%
BIOEQUIVALENCY AMENDMENT

Dear Sir or Madam:

Enclosed please find Taro Pharmaceuticals' Bioequivalence Amendment for Terconazole Vaginal Cream, 0.8%

As required by 21 CFR 314.96(d)(5), Taro is forwarding a copy of technical data (including 356h form). Taro Pharmaceuticals U.S.A. Inc. hereby certifies that this field copy is a true copy of the information submitted to the OGD.

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely
TARO PHARMACEUTICALS U.S.A., INC.

Teresa Jung for
Kalpana Rao
Vice-President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 02 2001
OGD

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

Taro Pharmaceuticals U.S.A., Inc.

July 31, 2001

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

Re: ANDA # 75-953
Terconazole Vaginal Cream, 0.8%
BIOEQUIVALENCY AMENDMENT

Dear Sir or Madam:

Reference is made to our Abbreviated New Drug Application submitted on August 31, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

Reference is also made to the comments received from the Agency's letter dated July 25th 2001 in reference to our request a meeting with the Agency to discuss the bioequivalence deficiency letter dated June 6, 2001.

We appreciate the Agency's comments to our clinical bioequivalence study. Because of the impact of the additional patient exclusions identified by the Agency in the June 6th deficiency letter, the original study now does not have adequate power and we must simply repeat the study.

In response to the Agency's comments and the suggestion that we submit a protocol for review, we are providing the following protocol for a bioequivalence study comparing Taro's Terconazole Vaginal Cream 0.8% product with that of the Ortho originator, product, Terazol® 3 (Attachment 1). This protocol has been modified to incorporate the Agency's comments about our original protocol submitted with our ANDA # 75-953.

We believe that we have addressed all the agency's comments about the protocol found in the deficiency letter of Terconazole Vaginal Cream, 0.8%. We have corrected all the discrepencies (and resulting confusion) between the terminology used in the protocol and the terminology used in the Case Report Form. We have also included an intention to treat analysis as requested (page 15 of 21 of the attached protocol).

In addition to the discussion of the protocol, the Agency also asked for an explanation of the high correlation between positive KOH preparation and positive fungal culture found in our prior study. *(Comment 9 of July 25th Agency's letter: In most VVC studies, approximately 20 to 30% of patients enrolled with a positive KOH are not eligible for the study because their fungal culture is negative or they have evidence of either bacterial vaginosis or trichomonas infection. In your study, only 2 of 170 (1.2%) enrolled patients had a negative fungal culture. Please explain your low rate of negative fungal culture and positive KOH.)*

To explain the high correlation between positive KOH and positive culture found in our study, we are enclosing Dr.———'s review of KOH and Culture techniques employed in his laboratory (Attachment 2). ————, M.D. is the Head of the Division of Infectious Diseases and Chief of the Department of Microbiology at the ———— Hospital where all our microbiology was conducted.

This amendment is being submitted in two copies, a third (Field copy) is also enclosed.

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,
TARO PHARMACEUTICAL U.S.A., INC.

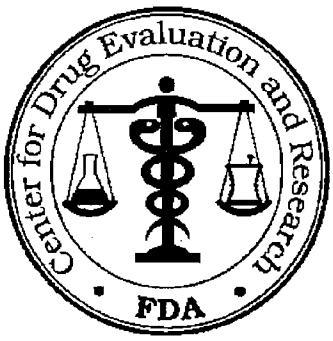
Teresa Sung for
Kalpana Rao
Vice-President, Regulatory Affairs

MINOR AMENDMENT

ANDA 75-953

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

AUG - 2 2001



TO: APPLICANT: Taro Pharmaceuticals USA Inc. TEL: (914)345-9001

ATTN: Kalpana Rao FAX: (914)345-8728

FROM: Sarah Ho PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 8, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

Reference is also made to your amendment(s) dated: May 22 and July 3, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__/__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC comments included.

AUG - 2 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-953 **APPLICANT:** Taro Pharmaceuticals USA Inc.

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

The deficiencies presented below represent a MINOR deficiency.

Bioequivalence for this drug product has not been established. Please refer to the deficiencies from the Division of Bioequivalence dated June 6, 2001. Please do not respond to this communication until all outstanding Bioequivalence deficiencies have been addressed.

Sincerely yours,

Paul Schwartz for

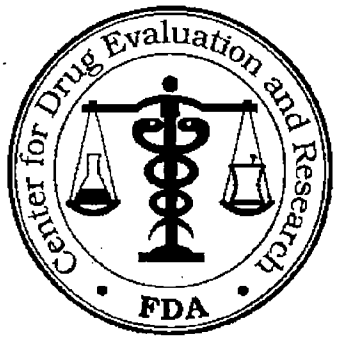
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

ANDA 75-953

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 24 2001



TO: APPLICANT: Taro Pharmaceuticals U.S.A., Inc. TEL: 914-345-9001

ATTN: Kalpana Rao FAX: 914-593-0078

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on July 31, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

OCT 24 2001

BIOEQUIVALENCY COMMENTS

ANDA: # 75-953 APPLICANT: Taro Pharmaceuticals

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

The Division of Bioequivalence has completed its review of your protocol submission acknowledged on the cover sheet. The protocol has been reviewed and we have the following comments:

1. The recommended times for follow-up visits are at Day 7 to 10 and Day 21 to 30.

2. The visit windows in the protocol are too large and should be modified according to comment #1.

3. The study entry criteria should include both clinical signs and symptoms as outlined in the protocol AND a positive KOH.

4. Patients who do not have a positive fungal culture should be excluded from both the MITT and the evaluable populations.

5. Compliance for a three-day treatment is considered to be taking the medication all three days. You should identify how compliance with treatment will be monitored. Compliance should be included in the evaluable patient definition.

6. No sample size calculation has been provided. The rate of negative fungal culture can be as high as 20%.

Sincerely yours,

Dale P. Conner

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

CC: ANDA # 75-953
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ Reviewer: Mary Fanning

Endorsements: (Draft and Final with Dates)
HFD-600/Mary Fanning Mary 10/3/01
HFD-650/Rabi Patnaik 9/10/2001
HFD-650/Lizzie Sanchez
HFD-650/Steven Mazzella
HFD-650/Dale Conner 10/11/01

V:\firmsnz\taro\ltrs&rev\75-953b

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 31 JUL 2001

5. **Protocol** (PRO) Strengths: 0.8%

Outcome: UN

Outcome Decisions: **UN** - Unacceptable

WinBio Comments: STA - Unacceptable

APPEARS THIS WAY
ON ORIGINAL

December 3, 2002

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AB

Re: Terconazole Vaginal Cream, 0.8%
ANDA #75-953
Bioequivalence Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Terconazole Vaginal Cream, 0.8% submitted August 31, 2000, and to the Agency's correspondence of June 6, 2001 and Taro's correspondence of July 31, 2001.

Based upon these correspondence, it was determined that the bioequivalence study needed to be repeated. As such, a new lot of Terconazole Vaginal Cream, 0.8% was manufactured (lot # S17252855) and study #TRCZ8R0104 was conducted. The results of this study are included herein, along with a diskette containing the SAS files. Please note that the CMC information about the new lot is being submitted to the Agency under separate cover.

This concludes our response to the Agency's bioequivalence deficiency letter of June 6, 2001.

If there are any questions regarding this application, or if additional information is required, please contact me at (914) 345-9001 x 298.

Sincerely,

12/3/02

Kalpana Rao
Vice President, Regulatory Affairs

RECEIVED
DEC 0 4 2002
OGD / CDER

5 Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

December 3, 2002

Office of Generic Drugs, CDER
Food and Drug Administration
Document control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/A

953

Reference: **ANDA 75-~~886~~- Terconazole Vaginal Cream, 0.8%**
Bioequivalence Amendment - Chemistry, Manufacturing and Controls Information

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) for Terconazole Vaginal Cream 0.8% submitted August 31, 2000, and to the amendments submitted October 26, 2000, May 22, 2001 and July 3, 2001 and to the Agency's correspondences of June 6, 2001 (Bioequivalency Amendment Letter) and August 2, 2001 (Minor Amendment Letter). Reference is also made to Taro's Bioequivalence Amendment submitted July 31, 2001 which indicated that a second clinical study would be performed to establish the bioequivalence of Taro's Terconazole Vaginal Cream, 0.8% to Terazol® 3 Vaginal Cream manufactured by Ortho Pharmaceutical Corporation.

The new clinical study has been conducted as per the guidelines stipulated in 21 CFR 320.38 and 320.63. A copy of the second study, Report No. TRCZ8R0104 is provided under a separate cover.

Clinical study TRCZ8R0104 was conducted using a new batch of Terconazole Vaginal Cream, 0.8% (L) S172-52855 (date of manufacture: July 6, 2001). This batch was manufactured according to the same master formula and manufacturing directions as the exhibit/biobatch of Terconazole Vaginal Cream, 0.8% submitted in the original application, however the scale was increased to ——— from ———.

In support of the new exhibit batch, we are submitting the following Chemistry Manufacturing and Controls (CMC) documentation:

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 www.taropharma.com

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

12/3/2002 TARO LETTER

MINOR AMENDMENT

ANDA 75-953

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JAN 30 2003

TO: APPLICANT: Taro Pharmaceuticals USA, Inc. TEL: 914-345-9001

ATTN: Kalpana Rao FAX: 914-~~345-8728~~ 593-0078

FROM: Wanda Pamphile PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

Reference is also made to your amendment(s) dated: December 3, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (_1_ page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in your response.

JAN 30 2003

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-953 **APPLICANT:** Taro Pharmaceuticals USA Inc.

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiency

Please reinstate specification and limit for the ——— ——— in your revised drug substance specifications.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comments in the response.

1. Please correct the following typographical errors:

   a. On page 3 of your cover letter you stated a limit for——— of NMT ———.

   b. The Test Date for the 3-month test station in your accelerated condition Stability Evaluation Summary, on page 33, is November 22, 2002.

   c. In your December 3, 2002 amendment for Chemistry, Manufacturing and Controls information, the cover letter and 356h form referenced an incorrect ANDA number (75-866). In the future, please reference the correct ANDA number in your submission.

2. The bioequivalence portion of your application is under review. Deficiencies, if any, will be communicated to you under a separate cover.

3. Please submit all available room temperature stability data.

Sincerely yours,

Paul Schwartzfer

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

February 28, 2003

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs, CDER
Food and Drug Administration
Document control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NDA

Re: ANDA 75-953
Terconazole Vaginal Cream, 0.8%
Minor Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) for Terconazole Vaginal Cream 0.8% submitted August 31, 2000, and to the amendments submitted October 26, 2000, May 22, 2001, July 3, 2001, July 31, 2001 and December 3, 2002 and to the Agency's correspondence of January 30, 2003 (Minor Amendment Letter).

The agency's comments have been restated and are followed by our response:

A. Deficiency
Please reinstate specification and limit for the ———— in your revised drug substance specifications.

Response
The specification and limit for ———— has been reinstated in the revised drug substance specifications. The revised specification is provided in Attachment 1.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comments in the response.
1. Please correct the following typographical errors:
a. On page 3 of your cover letter you stated a limit for ———— of NMT ———— .
b. The Test Date for the 3-month test station in your accelerated condition Stability Evaluation Summary, on page 33 is November 22, 2002.
c. In your December 3, 2002 amendment for Chemistry, Manufacturing and Controls information, the cover letter and 356h form referenced an incorrect ANDA number (75-886). In the future, please reference the correct ANDA number in your submission.

Response
Please note that we acknowledge the following typographical errors:
a. On page 3 of the cover letter to our December 3, 2002 amendment for Chemistry, Manufacturing and Controls information the limit for ———— was incorrectly stated as NMT———— . Please note that the correct limit is NMT ————

RECEIVED
MAR 0 3 2003
OGD / CDER

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

b. The Test Date for the 3-month test station in the accelerated condition Stability Evaluation Summary, on page 33 of the December 3, 2002 amendment for Chemistry, Manufacturing and Controls information was corrected from November 22, 2002 to November 22, 2001. The revised Stability Evaluation Summary is included in Attachment 2.

c. The cover letter and 356h form of our December 3, 2002 amendment for Chemistry, Manufacturing and Controls information had referred to an incorrect ANDA number. In the future, we will reference the correct ANDA number (75-953) in our submission and we apologize for any inconvenience this may have caused.

2. *The bioequivalence portion of your application is under review. Deficiencies, if any, will be communicated to you under a separate cover.*

Response

We note and acknowledge that the bioequivalence portion of our application is under review. Deficiencies, if any, will be communicated to us under a separate cover.

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

Response

Presented in Attachment 3 are 12 months of room temperature (long term) stability data for the clinical batch (L) S172-52855 and 36 months for the batch, (L) S172-51910, submitted in the original ANDA.

This completes our response to the Minor deficiency letter of January 30, 2003. If there are any questions regarding this amendment, or if additional information is required, please contact the undersigned at:

Taro Pharmaceuticals USA, Inc.
5 Skyline Drive,
Hawthorne, NY 10532
(914) 345-9001 Ext. 298

Sincerely yours,

2/28/03

Kalpana Rao
Vice President, Regulatory Affairs

May 21, 2003

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AF FPL

Re: **ANDA 75-953**
Terconazole Vaginal Cream, 0.8%
Labeling Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Terconazole Vaginal Cream, 0.8% on August 31, 2000. Reference is also made to the Agency's labeling deficiency letter dated May 12, 2003.

Comment:
Due to changes in the labeling for the reference listed drug, (Terazol®3 by Johnson & Johnson NDA 19-964/S-011 & S-014; revised March 2001; approved March 11, 2003), please revise your labeling to be in accord with the attached labeling.

Response:
Per the Agency's request, we have revised our labels and labeling to be in accord with the labeling changes for the reference listed drug Terazol®3.

Enclosed please find:

- **12 – Final Printed 20 g tubes**
- **12 – Final Printed 20 g cartons (w/1 applicator)**
- **12 – Final Printed 20 g cartons (w/3 applicators)**
- **12 – Final Printed Package Inserts/Patient Information Leaflets (1 applicator)**
- **12 – Final Printed Package Inserts/Patient Information Leaflets (3 applicators)**

In addition, and in accordance with 21 CFR 314.94(a)(8)(iv), we have included a side-by-side comparison of our previously submitted labels, labeling and package insert.

This concludes our Response to the Agency's labeling deficiency letter dated May 12, 2003. Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

Kalpana 5/21/03
Kalpana Rao
Vice-President, Regulatory Affairs

RECEIVED
MAY 22 2003
OGD / CDER

MEMORANDUM

To: ANDA 75-953
Drug: Terconazole Vaginal Cream, 0.8%

Sponsor: Taro Pharmaceuticals USA, Inc.
Kalpana Rao (914-345-9001 X298)

From: Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

8/18/03

Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

Date: August 18, 2003
Re: Request for Information

In order to complete the review of a bioequivalence study with clinical endpoints for ANDA 75-953 (TRCZ8R-0104), please submit the following information:

1. Please provide a new SAS data set and include in line listings the outcome (clinical success/failure, mycological success/failure, therapeutic success/failure) and patient population (Intent-to-Treat vs. Per Protocol) for each patient. One line summary data set should include the following variables for each patient per visit if data exist:

   - Center/site, patient/subject number, treatment group
   - ITT (yes/no), reason for exclusion from ITT
   - PP (yes/no), reason for exclusion from PP
   - Race, sex, age
   - Visit number, date of visit, days from baseline
   - Individual and total clinical signs and symptom scores for each visit
   - Therapeutic response (cure/failure)
   - Clinical response (cure/failure)
   - Mycological response (positive/negative)
   - Nugent score at baseline
   - Reason for discontinuation
   - Compliance

   All SAS transport files should use .xpt as the file extension and should not be compressed.

2. Provide a copy of Case Report Form (CRF) for the following patients:

   #157, 304, 606, 609, 714, 724, 726, 838, 926, 949

3. No patient was identified with a negative baseline fungal culture in your study. Please provide detailed information about the screening process, the timing of enrollment related to the receipt of a positive fungal culture and why your negative baseline culture rate is zero.

4. Not all databases listed under "Data Dictionary" were submitted. If you have electronic databases available, please submit them for the review (vol. 3.1, pp. 126-133).

August 21, 2003

Office of Generic Drugs
Attention: Document Control Room
Metro Park North II, FDA
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Taro Pharmaceuticals U.S.A., Inc.

ORIG AMENDMENT
N/AE

Ref: **ANDA 75-953 (TRCZ8R-0104)**
Terconazole Vaginal Cream, 0.8%

Bioequivalence Amendment - Response to the letter dated August 18, 2003

Dear Sir/Madam:

Reference is made to our ANDA for Terconazole Vaginal Cream, 0.8%, and the correspondence dated August 18, 2003, in which following information was requested for the completion of the review of bioequivalence study.

Requested information:

1. *Please provide a new SAS data set and include in line listings the outcome (Clinical success/failure, mycological success/failure, therapeutic success/failure) and patient population (Intent-to-Treat vs. Per Protocol) for each patient. One line summary data set should include the following variables for ech patient per visit if data exist:*

    - *Center/Site, patient/subject number, treatment group*
    - *ITT (yes/no), reason for exclusion from ITT*
    - *PP (yes/no), reason for exclusion from PP*
    - *Race, sex, age*
    - *Visit number, date of visit, days from baseline*
    - *Individual and total clinical signs and symptom scores for each visit*
    - *Therapeutic response (cure/failure)*
    - *Clinical response (cure/failure)*
    - *Mycological response (positive/negative)*
    - *Nugent score at baseline*
    - *Reason for discontinuation*
    - *Compliance*

All SAS transport files should use .xpt as the file extension and should not be compressed.

Response:

We are submitting a new SAS data set in Attachment 1, as requested by the Agency. This set provides for all the requested information required for the review purpose. Please also note that all the SAS files are with .xpt extension and were not compressed (floppy disk 1). We are also including a hard copy of the files for reviewer's convenience in Attachment 1.

2. *Provide a copy of Case Report Form (CRF) for the following patients: #157, 304, 606, 609, 714, 724, 726, 838, 926, 949*

Response:

Included herein in the Attachment 2 is the copy of Case Report Form for the following patients:

#157, 304, 606, 609, 714, 724, 726, 838, 926, 949

3. *No patient was identified with a negative baseline fungal culture in your study. Please provide detailed information about the screening process, the timing of enrollment related to the receipt of a positive fungal culture and why your negative baseline culture rate is zero.*

Response:

The following is the screening process:

During the screening process, any patient with signs and symptoms of vaginal candidiasis, after obtaining proper consent, had her vaginal secretions sampled. The sample was immediately transported to the laboratory.

At the laboratory, a potassium hydroxide 10% (KOH) smear was made and read by the microbiologist. Patients with identified pseudohyphae, hyphae, or budding yeasts were cultured and enrolled into the study Patients with negative KOH smears were not enrolled into the study.

Our experience with this test has been that in the context of a symptomatic patient and a positive gynecologic examination, a KOH preparation prepared and read by an experienced microbiologist should only rarely yield a false positive result.

4. *Not all databases listed under :Data Dictionary" were submitted. If you have electronic databases available, please submit them for the review. (vol. 3.1, pp 126-133)*

Response:

We are submitting the electronic data bases in the attachment 3 for the review. (please see floppy disk 2)

This concludes our Bioequivalence Amendment. If there are any questions, or if you require additional information, please do not hesitate to contact us at:

Taro Pharmaceuticals U.S.A., Inc.
Attn: Kalpana Rao, VP, Regulatory Affairs, USA
Five Skyline Drive, Hawthorne, New York 10532
(914) 345-9001

Sincerely,
Taro Pharmaceuticals Inc.

KR 8/21/03
Kalpana Rao
VP, Regulatory Affairs, USA

September 4, 2003

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

Re: ANDA 75-953
Terconazole Vaginal Cream, 0.8%
Resubmission of Electronic Files

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Terconazole Vaginal Cream, 0.8% on August 31, 2000. Reference is also made to Taro's Bioequivalence submission of August 21, 2003 and to the Agency's faxed request for resubmission of the electronic data, dated August 29, 2003.

RESUBMISSION REQUIRED if any of the following are checked

	Document(s) submitted in non archival format (MS Word, etc.) – documents other than draft labeling text, should only be submitted in PDF format described in the guidance(s).
	Data set(s) submitted in non archival format(s) – SAS transport V5 as per SAS TS-140 (XPORT) is the format specified by the guidance.
	Other *Please, Only send Bioequivalence data in .xpt and/or .pdf formats.*

Response:
The data set has been revised to SAS transport files (using XPORT format) and this is included on the enclosed disk.

This concludes our Response to the Agency's request for electronic resubmission letter dated August 29, 2003. Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

9/4/03
Kalpana Rao
Vice-President, Regulatory Affairs

RECEIVED
SEP 08 2003
OGD/CDER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland
FDA

Date: 05March2004

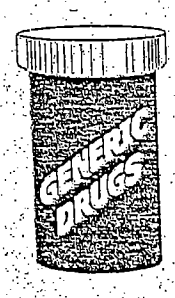
To: Kalpana Rao

Phone: 914 345 9001 x6298 Fax: 914 593 0078

From: Krista Scardina

Phone: (301) 827-5845 Fax: (301) 594-0183

Number of Pages: 3
(Including Cover Sheet)



Comments: Please Note: The comments attached are for your information only. No responce is needed.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-953 APPLICANT:Taro Pharmaceuticals, Inc.

DRUG PRODUCT: Terconazole Vaginal Cream, 0.8%

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

The data submitted to ANDA 75-953, using the primary endpoint of therapeutic cure rate at the test-of cure visit (Visit 3, days 21-30), are adequate to demonstrate bioequivalence of Taro Pharmaceuticals Inc.'s Terconazole Vaginal Cream, 0.8%, with the reference listed drug, Ortho McNeil Pharmaceuticals' Terazol® Vaginal Cream, 0.8%.

1. Please note that patients that were considered a clinical cure (any sign or symptom that was a 1 or 2 at baseline is 0 (absent), and any sign or symptom with a baseline score of 3 (severe) is 0 or 1) and had eradication of fungal culture (negative KOH and negative culture) at visit 3 (primary endpoint) were considered as a therapeutic cure. All scores for vaginal discharge were disregarded, as this sign cannot be consistently correlated with the presence or absence of *Vulvovaginal Candidiasis (VVC)*. Mycological cure was evaluated only at the test-of-cure visit (Visit 3).

2. The Division of Scientific Investigation recommends you provide a sealed code for use by FDA and maintain it at each testing facility for all future bioequivalence studies. It is your responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested. Please refer to "Handling and Retention of BA and BE Testing Samples", posted 8/20/02 for details.

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,

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

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

ANDA 75-953

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 17 2004

APPLICANT: Taro Pharmaceuticals U.S.A., Inc. TEL: 914-345-9001

ATTN: Kalpana Rao FAX: 914-593-0078

FROM: Wanda Pamphile PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terconazole Vaginal Cream, 0.8%.

Reference is also made to your amendment(s) dated: February 28, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in your response.

WP 3/17/04

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

3/17/2004 FDA FAX

March 22, 2004

Taro Pharmaceuticals U.S.A., Inc.

Wanda Pamphile
Project Manager
Division of Chemistry I
Office of Generic Drugs
CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

RE: ANDA: 75-953- Minor Amendment
Terconazole Vaginal Cream 0.8%

Dear Ms. Pamphile,

Reference is made to our Abbreviated New Drug Application for the above-referenced product dated August 31, 2000 and to the minor amendment dated February 28, 2003.

Reference is also made to the agency's minor amendment letter dated March 17, 2004, in which the application was deemed deficient. For ease of review the deficiencies presented in the letter have been restated and are followed by our responses.

A. Deficiencies:

1. *Drug Master File (DMF) No. ——— is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.*

Response
Taro has been notified that the DMF holder ———————— has submitted a complete response to their DMF deficiencies. This notification is provided in Attachment 1.

2. *Regarding the finished product release specifications, we have the following comments:*

i. [redacted]

ii. [redacted]

Response
The finished product release specifications have been revised to include ———

[redacted]

RECEIVED
MAR 23 2004
OGD/CDER

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

3/22/2004 TARO LETTER

Taro Pharmaceuticals U.S.A. Inc.
ATT. Kalpana Rao
Vice President, Regulatory Affairs USA
5 Skyline Drive,
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,

N. Rao

for Kalpana Rao
Vice President, Regulatory Affairs USA

APPEARS THIS WAY
ON ORIGINAL