

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 77-511

Name: Terbinafine Hydrochloride Cream, 1%

Sponsor: Taro Pharmaceuticals

Approval Date: July 2, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-511

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-511

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-511

Taro Pharmaceuticals U.S.A., Inc.
Attention: Sirinivasa Rao
Director Regulatory Affairs
3 Skyline Drive
Hawthorne, NY 10532

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 30, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terbinafine Hydrochloride Cream, 1%.

Reference is also made to the tentative approval letter issued by this office on March 22, 2006, and to your amendments dated October 4, 2006; and March 30, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective the date of this letter. The Division of Bioequivalence has determined your Terbinafine Hydrochloride Cream, 1%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Lamisil® Cream of Novartis Pharmaceutical Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

We remind you of your commitment specified in your amendment dated June 25, 2007. To alert the Office of Generic Drugs staff that you are submitting information to address the post-approval commitment, please state "Post- Approval Commitment Response" at the top of your cover letter.

Sincerely yours,

(See appended electronic signature page)

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Gary Buehler

7/2/2007 09:09:53 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-511

TENTATIVE APPROVAL LETTER

ANDA 77-511

MAR 22 2006

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 December 30, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terbinafine Hydrochloride Cream, 1%.

Reference is also made to your amendments dated August 23, 2005, and March 21, 2006.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of the patent/exclusivity issue noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Lamisil® Cream of Novartis Consumer Health Inc. is currently subject to a period of patent protection. As noted in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 4755534 (the '534 patent) is scheduled to expire on December 30, 2006. Your application contains a Paragraph III Certification to the '534 patent under Section 505(j)(2)(A)(vii)(III) of the Act. This certification states that Taro Pharmaceuticals U.S.A. Inc. (Taro) will not market this Terbinafine Hydrochloride Cream prior to the



your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '534 patent has expired, i.e., December 30, 2006.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

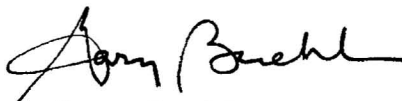
Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the ANDA and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may also lead to a delay in the issuance of the final approval letter.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final

approval letter prior to December 30, 2006, you should amend your application accordingly.

For further information on the status of this application or upon submitting an amendment to the application, please contact Benjamin Danso, Pharm.D, Project Manager, at 301-827-5848.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Gary Buehler". The signature is fluid and cursive, with the first name "Gary" and last name "Buehler" clearly distinguishable.

Gary Buehler

Director

3/22/06

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 77-511
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

W. Pichman
3/22/06

Endorsements:

HFD-629/K.Woodland/ *K Woodland 1/23/06*
HFD-623/R.Bykadi/ *S. Bykadi 1-24-2006*
HFD-617/B.Danso/ *BD 1-24-06*
HFD-613/R.Wu/ *via Email 1-23-06*
HFD-613/J.Grace/ *via Email 1-24-06*

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E/T by

TENTATIVE APPROVAL

ps 1/31/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-511

LABELING

**ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS**

(b) (4)



**ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS**

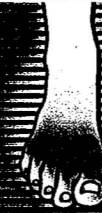
(b) (4)



Cures Most Athlete's Foot

Compare to the
active ingredient
in Lamisil AT®*

Terbinafine Hydrochloride Cream 1% Antifungal Cream



- Relieves Itching & Burning
- Full Prescription Strength

Cures Most Athlete's Foot

Full Prescription Strength

Terbinafine Hydrochloride Cream 1% Antifungal Cream

NET WT 0.42 oz (12 g)

Terbinafine
Hydrochloride
Cream 1%
Antifungal Cream



Drug Facts (continued)
Inactive ingredients: benzyl alcohol, cetyl alcohol, cetyl palmitate, isopropyl myristate, polyacrylate 60, purified water, sodium hydroxide, sorbitan monostearate, stearyl alcohol.

TERBINAFINE
Hydrochloride
Cream 1%
Antifungal Cream

Drug Facts
Terbinafine hydrochloride 1%
Active ingredient
Purpose
Antifungal
This product is not manufactured by Hoechst Celanese Corporation, Kansas City, MO. It is a generic product of Taro Pharmaceuticals, Inc., Fort Lauderdale, FL 33304.
Warnings For external use only.
• Do not use on nails or scalp. • If in or near the mouth or the eyes. • For vaginal yeast infections.
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or gets worse.
Keep out of reach of children. If swallowed, get medical help or contact a poison control center.
Night away.
Directions
• adults and children 12 years and older
• use the tip of the cap to break the seal and open the tube
• wash the affected skin with soap and water and dry completely before applying
• for athlete's foot wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
• between the toes only apply twice a day (morning and night) for 1 week or as directed by a doctor.
• on the bottom or sides of the feet apply twice a day (morning and night) for 2 weeks or as directed by a doctor.
• for foot and nail ringworm apply once a day (morning or night) for 1 week or as directed by a doctor.
• wash hands after each use
• children under 12 years: ask a doctor
Other information
• do not use if seal on tube is broken or is not viable
• store at controlled room temperature 20°-25°C (68°-77°F)
• see carton or tube crimp for lot number and expiration date

ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS

(b) (4)

Compare to the
active ingredient
in Lamisil AT®*

Cures Most Athlete's Foot

Terbinafine Hydrochloride Cream 1% Antifungal Cream



- Relieves Itching & Burning
- Full Prescription Strength

LPK-0000-0
0505-0
M000

T 27

Cures Most Athlete's Foot

Full Prescription Strength

Terbinafine Hydrochloride Cream 1% Antifungal Cream

NET WT 1/2 oz (15 g)

Terbinafine
Hydrochloride
Cream 1%
Antifungal Cream



Drug Facts (continued)
Inactive ingredients: benzyl alcohol, cetyl alcohol, cetyl palmitate, isopropyl myristate, polysorbate 80, purified water, sodium hydroxide, sorbitan monolaurate, stearyl alcohol.

1180802127915

TERBINAFINE
HYDROCHLORIDE
CREAM 1%
ANTIFUNGAL CREAM
L.P.K. PHARMACEUTICALS
NEW YORK, NY 10022
MADE IN CANADA

TERBINAFINE
HYDROCHLORIDE
CREAM 1%
ANTIFUNGAL CREAM
L.P.K. PHARMACEUTICALS
NEW YORK, NY 10022
MADE IN CANADA

Terbinafine
Hydrochloride
Cream 1%
Antifungal

Drug Facts

Active ingredient
Terbinafine hydrochloride 1%

Purpose
Antifungal

Uses
• cures most athlete's foot (tinea pedis)
• cures most itch (tinea cruris) and ringworm (tinea corporis)

Warnings
For external use only
• relieves itching, burning, cracking and scaling which accompany these conditions

The way to use
• on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or gets worse.
Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.

Directions
• adults and children 12 years and older
• use the tip of the cap to break the seal and open the tube
• wash the infected skin with soap and water and dry completely before applying
• for athlete's foot wear with-thing, ventilated shoes. Change shoes and socks at least once daily.
• between the toes only; apply twice a day (morning and night) for 1 week or as directed by a doctor.
• on the bottom or sides of the feet: apply twice a day (morning and night) for 2 weeks or as directed by a doctor.
• for lock heel and ringworm: apply once a day (morning or night) for 1 week or as directed by a doctor.
• wash hands after each use
• children under 12 years: ask a doctor

Other information
• do not use if seal on tube is broken or is not visible
• store at controlled room temperature 20°-25°C (68°-77°F)
• see carton or tube crimp for lot number and expiration date

Illustrations:
• Foot with athlete's foot symptoms
• Application of cream to the foot

ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS

(b) (4)

(b) (4)

7/8" DIAMETER
MASTER TEMPLATE

(b) (4)

Cures Most Athlete's Foot Full Prescription Strength
Terbinafine Hydrochloride
Cream 1%
Antifungal Cream NET WT 1/2 oz (15 g)

Active ingredient	Purpose	Directions
Terbinafine hydrochloride 1% Indications • cures most athlete's foot (tinea pedis) • cures most jock itch (tinea cruris) and ringworm (tinea corporis) • relieves itching, burning, cracking and scaling which accompany these conditions Warnings For external use only. Do not use • on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections. When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water. Stop use and ask a doctor if too much irritation occurs or gets worse. Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away. Store at controlled room temperature 20°-25°C (68°-77°F). See crimp of tube for lot number and expiration date.	Antifungal	• adults and children 12 years and older • use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • for athlete's foot wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. • between the toes only: apply twice a day (morning and night) for 1 week or as directed by a doctor. • on the bottom or sides of the feet: the first apply twice a day (morning and night) for 2 weeks or as directed by a doctor. • for jock itch and ringworm: apply once a day (morning or night) for 1 week or as directed by a doctor. • wash hands after each use • children under 12 years: ask a doctor

Dist. by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 Made in Canada
LPI-0000-0 0595-0 000

(b) (4)

ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS

(b) (4)

Cures Most Athlete's Foot

Terbinafine Hydrochloride Cream 1% Antifungal Cream

Compare to the active ingredient in Lamisil AT®*



- Relieves Itching & Burning
- Full Prescription Strength

LPK-0000-6
0305-0
M000

T30

Cures Most Athlete's Foot

Full Prescription Strength

Terbinafine Hydrochloride Cream 1% Antifungal Cream

NET WT 0.85 oz (24 g)

Terbinafine Hydrochloride Cream 1% Antifungal Cream



Drug Facts (continued)
Other Information
• Do not use if seal on tube is broken or is not visible
• Store at controlled room temperature 20°-25°C (68°-77°F)
• See carton or tube crimp for lot number and expiration date
Inactive Ingredients: benzyl alcohol, cetyl palmitate, isopropyl myristate, polyethylene glycol, purified water, sodium hydroxide, sorbitan monostearate, stearyl alcohol.

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NO COLOR



Drug Facts
Active ingredient
Terbinafine hydrochloride 1%
Purpose
Antifungal
Uses
• Cures most athlete's foot (tinea pedis)
• Relieves itching, burning, cracking and scaling which accompany these conditions
Warnings
For external use only
Do not use • on rash or scalp • at or near the mouth or the eyes • for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.
Stop use and ask a doctor if top much redness occurs or gets worse.
Directions
• Adults and children 12 years and older
• Use tip of the cap to break the seal and open the tube
• Wash the affected area with soap and water and dry completely before applying
• Rub the cream into the skin. Change shoes and socks at least once daily.
• Between the toes only: apply twice a day (morning and night) for 1 week or as directed by a doctor.
• On the bottom of the foot: apply twice a day (morning and night) for 1 week or as directed by a doctor.
• For jock itch and ringworm: apply once a day (morning or night) for 1 week or as directed by a doctor.
• Wash hands after each use
• Children under 12 years: ask a doctor

Cures Most Athlete's Foot
Antifungal Cream

ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS

(b) (4)

(b) (4)

7/8" DIAMETER
MASTER TEMPLATE

(b) (4)

Cures Most Athlete's Foot

Terbinafine Hydrochloride
Cream 1%
Antifungal Cream

NET WT 0.85 oz (24 g)

Active Ingredient	Purpose	Directions
Terbinafine Hydrochloride 1%.....	Antifungal	• adults and children 12 years and older
Uses • cures most athlete's foot (tinea pedis) • cures most jock itch (tinea cruris) and ringworm (tinea corporis) • relieves itching, burning, cracking and scaling which accompany these conditions		• use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • for athlete's foot wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. • between the toes only: apply twice a day (morning and night) for 1 week or as directed by a doctor. • on the bottoms or sides of the feet: apply twice a day (morning and night) for 2 weeks or as directed by a doctor. • for jock itch and ringworm: apply once a day (morning or night) for 1 week or as directed by a doctor. • wash hands after each use • children under 12 years: ask a doctor
Warnings For external use only. Do not use: • on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections. Always using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water. Stop use and ask a doctor if too much irritation occurs or gets worse. Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.		
Store at controlled room temperature 20°-25°C (68°-77°F) See crimp of tube for lot number and expiration date		

Dist. by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 Made in Canada
UPK-0000-0 0505-0 000

(b) (4)

(b) (4)

**ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS**

(b) (4)

Compare to the
active ingredient
in Lamisil AT®*

**Terbinafine
Hydrochloride**
Cream 1%
Antifungal Cream



- **Relieves Itching & Burning**
- **Full Prescription Strength**

Full Prescription Strength

Terbinafine Hydrochloride

Cream 1%
Antifungal Cream

NET WT 1 oz (30 g)

Terbinafine Hydrochloride

Antifungal Cream



Drug Facts (continued)

Other information

do not use if seal on tube is broken or if you notice any other damage to the container

use caution or take steps for lot number and expiration date

keep out of reach of children. If you are pregnant, please consult your health care provider before using this product.

Keep this and all other medicines out of the reach of children. Poisoning may happen if a child takes too much of this medicine.

Do not use if you are allergic to any of the ingredients. Please see the "Warnings" section for a complete list of ingredients. At the time this medicine was prepared, the following ingredients were used: benzyl alcohol, methylparaben, propylparaben, polyethylene glycol, purified water, sodium hydroxide, and water.

**NO COPY
NO COLOR**

Distributed by:
Pharmaceuticals U.S.A., Inc.
New York, NY 10032
also Pharmaceuticals U.S.A., Inc.
in Canada



2 weeks on the bottom
or slides off the foot



individual center right away.

Drug Facts	Directions
Read the important information about this medicine carefully. Warnings: - Do not use if you are allergic to any of the ingredients. - Do not use if you are pregnant or breastfeeding. - Do not use if you are taking any other medicine. - Do not use if you are taking any other medicine. Directions: Apply a thin layer to the affected area 2 to 4 times a day. Other information: Keep this and all medicines out of the reach of children.	Directions: Apply a thin layer to the affected area 2 to 4 times a day. Other information: Keep this and all medicines out of the reach of children.

This product is not manufactured or distributed by Novartis Consumer Health, Inc., owner of the registered trademark Novartis A.T.

Antifungal Cream

Terbinafine Hydrochloride Cream 1%

**ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS**

(b) (4)

(b) (4)

(b) (4)

Cures Most Athlete's Foot

Full Prescription Strength

Terbinafine Hydrochloride

Cream 1%

Antifungal Cream

NET WT 1 oz (30 g)

Active ingredient
Terbinafine Hydrochloride 1%.....

Purpose
Antifungal

Directions
• adults and children 12 years and older
• use the tip of the cap to break the seal and open the tube
• wash the affected skin with soap and water and dry completely before applying
• for athlete's foot wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
• between the toes only: apply twice a day (morning and night) for 1 week or as directed by a doctor.
• on the bottom or sides of the feet: apply twice a day (morning and night) for 2 weeks or as directed by a doctor.
• for jock itch and ringworm: apply once a day (morning or night) for 1 week or as directed by a doctor.
• wash hands after each use
• children under 12 years: ask a doctor

Uses
• cures most athlete's foot (tinea pedis)
• cures most jock itch (tinea cruris) and ringworm (tinea corporis)
• relieves itching, burning, cracking and scaling which accompany these conditions

Warnings
For external use only.
Do not use:
• on nails or scalp
• in or near the mouth or the eyes
• for vaginal yeast infections.
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or gets worse.
Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.

Store at controlled room temperature 20°-25°C (68°-77°F)
See crimp of tube for lot number and expiration date



Dist. by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
LPK-0000-0 0505-0 000

Made in Canada.

(b) (4)

(b) (4)

ATTACHED LEGEND TO ALL
DIGITAL MECHANICALS

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-511

LABELING REVIEWS

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

ANDA Number: 77-511

Date of Submission: December 30, 2004 (e-submission)

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Terbinafine Hydrochloride Cream, 1% (OTC)

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. Revise "Terbinafine Hydrochloride 1% Cream" to read "Terbinafine Hydrochloride Cream 1%".
- b. In order for us to verify your compliance with the labeling format requirements of 21 CFR 201.66, please submit a format legend for each size of your container and carton labels.

2. CONTAINER (b) (4) 12 g, 15 g, 24 g, and 30 g tubes)

Refer to GENERAL COMMENTS

3. CARTON (one tube)

- a. Refer to GENERAL COMMENTS
- b. 12 g and 15 g Cartons: In the electronic submission, text is cut-off. Please realign the horizontal barlines (refer to attachment).

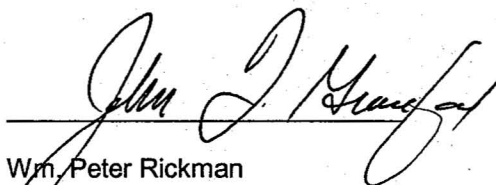
4. CONSUMER EDUCATIONAL BROCHURE

- a. Refer to GENERAL COMMENT 1.a.
- b. Picture #1: add the caption "1 week between the toes"

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

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/cdernew/listserv.html> or <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



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

Attachment: electronic submissions of the 12 g and 15 g Cartons

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 28 (checked 5/11/05)		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:

****First Generic****

- Labeling review based on the approved labeling for the OTC reference listed drug (Lamisil AT® Cream NDA 20-980.) The original application and labeling was approved March 9, 1999. There have been no labeling supplements approved since this date. However, a letter was issued by the New Drug division on October 26, 2000 requesting the following:
In the FEDERAL REGISTER of August 29, 2000 (65 FR 52302), the Food and Drug Administration (FDA) published an amendment of the final monograph for over-the-counter (OTC) topical antifungal drug products to make a minor change in the indications for these drug products. The change inserted the word "most" between the introductory phrase and the name of the condition(s) for which the OTC topical antifungal drug product is to be used."
- Packaging
The RLD packages product in 12 g, 24 g and 30 g tubes.
ANDA: (b) (4)
12 g, 15 g, 24 g, and 30 g (b) (4) tubes
Inner seal (b) (4) permanent seal
 - Lot number and expiration date will be stamped on the container labels at the time of print. [vol. B1.1, section 1.4.2, pg. 1]
 - Taro's 1-800 number will be provided prior to print for commercial use. [Vol. b1.1, section 1.4.2., pg. 1]
- Manufacturing facility [Vol. B1.4. section 3.2.P.3.1, pg. 1]
Taro Pharmaceuticals Inc.
130 East Drive,
Brampton, Ontario
Canada, L6T 1C1
- Inactive ingredients
There does not appear to be a discrepancy in inactives between the product labeling and the Component and Composition statements. [Vol. B1.2, section 2.3, pg. 16]
Purified water, Polysorbate, Cetyl alcohol, Steryl alcohol, Cetyl palmitate, Isopropyl myristate, Sorbitan Monosterate, Sodium hydroxide, Benzyl alcohol
- Storage
Not a USP item
RLD – Store at Controlled Room Temperature (20°-25°C (68°-77°F)
ANDA – Store at Controlled Room Temperature (20°-25°C (68°-77°F)

6. Patent and Exclusivity for NDA 20-980

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	How Filed	Labeling Impact
020980	001	4680291	JUL 14 2004	U-73	Expired	None
020980	001	4755534	DEC 30 2006	U-73	P III (V1.1, section 1.3.3, pg. 2)	None

Exclusivity Data

There is no unexpired exclusivity for this product.

7. Bioequivalence Issues – Pending review as of May 10, 2005

Date of Review: May 11, 2005 Date of Submission: December 30, 2004 (Original Submission)

Primary Reviewer: Ruby Wu RW Date: 5/11/05

Team Leader: John Grace JG Date: 5-11-05

cc: ANDA: 77-511
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\77511.na1.L.doc
Review

(b) (4)

(b) (4)



div.

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

ANDA Number:	77-511
Date of Submission:	May 25, 2005 (Amendment: e-submission)
Applicant's Name:	Taro Pharmaceuticals USA, Inc.
Established Name:	Terbinafine Hydrochloride Cream, 1% (OTC)

APPROVAL SUMMARY

1. Do you have Final Printed Labels and Labeling? Yes.
2. CONTAINER ^{(b) (4)} 12 g, 15 g, 24 g, and 30 g tubes)
Satisfactory in final print as of the May 25, 2005 e-submission.
^{(b) (4)}
12 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb12gT0000-0S.pdf
15 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb15gT0000-0S.pdf
24 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb24gT 0000-0S.pdf
30 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb30gT 0000-0S.pdf
3. CARTON (one tube)
Satisfactory in final print as of the May 25, 2005 e-submission.
^{(b) (4)}
12 g: \\Cdsesubogd1\N77511\N 000\2005-05-25\Terb12gC0000-0S.pdf
15 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb15gC0000-0S.pdf
24 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb24gC 0000-0S.pdf
30 g: \\CDSESUBOGD1\N77511\N 000\2005-05-25\Terb30gC 0000-0S.pdf
4. CONSUMER EDUCATIONAL BROCHURE
Satisfactory in final print as of the May 25, 2005 e-submission.
\\CDSESUBOGD1\N77511\N 000\2005-05-25\TerbInsert 0000-0S.pdf

Revisions needed post-approval: No.

BASIS OF APPROVAL

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Lamisil ® Cream (Same as OB...not modifier "AT")
NDA Number: 20-980
NDA Drug Name: Terbinafine Hydrochloride Cream, 1%
NDA Firm: Novartis
Date of Approval of NDA Insert and supplement: The original application and labeling was approved March 9, 1999.
There have been no labeling supplements approved since this date.
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 & Carton Labels: Side-by-side comparison with innovator labels in jacket.

Patent and Exclusivity for NDA 20-980

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	How Filed	Labeling Impact
020980	001	4680291	JUL 14, 2004	U-73	Expired	None
020980	001	4755534	DEC 30, 2006	U-73	P.III (V1.1, section 1.3.3, pg. 2)	None

Exclusivity Data

There is no unexpired exclusivity for this product.

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 28 (checked 7/13/05)		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:

First Generic

- Labeling review based on the approved labeling for the OTC reference listed drug (Lamisil AT® Cream NDA 20-980.) The original application and labeling was approved March 9, 1999. There have been no labeling supplements approved since this date. However, a letter was issued by the New Drug division on October 26, 2000 requesting the following:
In the FEDERAL REGISTER of August 29, 2000 (65 FR 52302), the Food and Drug Administration (FDA) published an amendment of the final monograph for over-the-counter (OTC) topical antifungal drug products to make a minor change in the indications for these drug products. The change inserted the word "most" between the introductory phrase and the name of the condition(s) for which the OTC topical antifungal drug product is to be used."
- Packaging
The RLD packages product in 12 g, 24 g and 30 g tubes.
ANDA: (b) (4)
12 g, 15 g, 24 g, and 30 g (b) (4) tubes
Inner seal (b) (4) permanent seal
 - Lot number and expiration date will be stamped on the container labels at the time of print. [vol. B1.1, section 1.4.2, pg. 1]
 - Taro's 1-800 number will be provided prior to print for commercial use. [Vol. b1.1, section 1.4.2., pg. 1]
- Manufacturing facility [Vol. B1.4. section 3.2.P.3.1, pg. 1]
Taro Pharmaceuticals Inc.
130 East Drive,
Brampton, Ontario
Canada, L6T 1C1
- Inactive ingredients
There does not appear to be a discrepancy in inactives between the product labeling and the Component and Composition statements. [Vol. B1.2, section 2.3, pg. 16]
Purified water, Polysorbate, Cetyl alcohol, Steryl alcohol, Cetyl palmitate, Isopropyl myristate, Sorbitan Monosterate, Sodium hydroxide, Benzyl alcohol
- Storage
Not a USP item
RLD – Store at Controlled Room Temperature (20°-25°C (68°-77°F)
ANDA – Store at Controlled Room Temperature (20°-25°C (68°-77°F)

6. Patent and Exclusivity for NDA 20-980

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	How Filed	Labeling Impact
020980	001	4680291	JUL 14, 2004	U-73	Expired	None
020980	001	4755534	DEC 30, 2006	U-73	P III (V1.1, section 1.3.3, pg. 2)	None

Exclusivity Data

There is no unexpired exclusivity for this product.

7. Bioequivalence Issues – Pending review as of July 13, 2005

Date of Review:	July 13, 2005	Date of Submission:	May 25, 2005 (Amendment)
Primary Reviewer:	Ruby Wu	Date:	
Team Leader:	John Grace	Date:	

cc: ANDA: 77-511
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\77511.OTC.ap.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-511

CHEMISTRY REVIEWS

#1
ANDA 77-511

Terbinafine Hydrochloride Cream, 1%

Taro Pharmaceuticals U.S.A., Inc.

**Kathy P. Woodland
Division of Chemistry I
Team 5**

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A. Reviewer's Signature	8
B. Endorsement Block	8
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Chemistry Review Data Sheet

1. ANDA 77-511
2. REVIEW #:1
3. REVIEW DATE: May 8, 2005
Revised June 10, 2005
4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

December 30, 2004

Acceptable for Filing

January 3, 2005

Amendment (add alternate source of drug substance)

March 9, 2005

Amendment (labeling)

May 26, 2005

7. NAME & ADDRESS OF APPLICANT:

Name: Taro Pharmaceuticals U.S.A.

Address: 5 Skyline Drive
Hawthorne, N.Y. 10532



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Kalpana Rao

Telephone: 914-345-9001

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Terbinafine Hydrochloride Cream, 1%

9. LEGAL BASIS FOR SUBMISSION:

- a. The basis of Taro's proposed ANDA for Terbinafine Hydrochloride Cream, 1% is the approved listed drug, Lamisil, NDA 20980, held by Novartis Consumer Health Inc.
- b. There is no unexpired exclusivity for Lamisil Cream, 1%. There is one patent #4755534, which will expire on Dec. 30, 2006.

10. PHARMACOL. CATEGORY: Treatment of Athlete's foot.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 10 mg/g (1%)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: ☐ Rx ☒ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

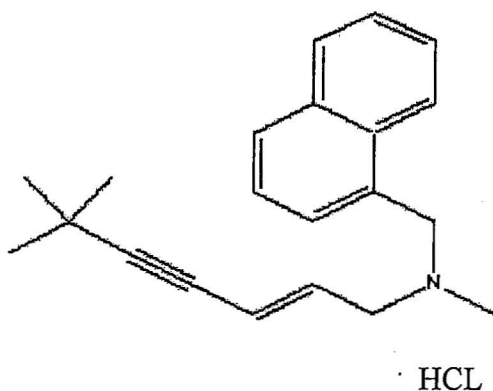
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

TRANS-N-(6,6-DIMETHYL-2-HEPTEN-4-YNYL)-N-METHYL-; Lamisil (free base);
Lamosil; 1-Naphthalenemethanamine, N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-, (E)-,
monohydrochloride;

Molecular Formula: $C_{21}H_{26}ClN$

Molecular Weight: 327.90



17. RELATED/SUPPORTING DOCUMENTS: None

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	5/10/04 B.Lim	
				1	Inadequate	6/7/005 K. Woodland	
				4			
				4			
				4			
				4			
				4			
				4			



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	Not Required		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-511

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This product is a FIRST GENERIC. Not approvable. Minor Chemistry, Labeling is deficient and Bioequivalence is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Terbinafine Hydrochloride drug substance is a white to off-white crystalline powder. The drug substance is soluble in methylene chloride and methanol; sparingly soluble in acetone, ethanol, 2-propanol; slightly soluble in water; practically insoluble in toluene.

Drug Product:

The product is

(b) (4)

The MDD is 40 mg/day. (30 g/7days x 1% x 1000mg/g). The IT is (b) (4)%, the QT is (b) (4)%.

B. Description of How the Drug Product is Intended to be Used

The drug product Terbinafine Hydrochloride Cream, 1% is an OTC product used for the treatment of Athlete's Foot (tinea pedis), jock itch (tinea cruris), and body ringworm (tinea corporis) (antifungal).

The treatment is one week for Athlete's Foot between the toes, jock itch, and body ringworm, and two weeks for Athlete's Foot on the bottoms or sides of the foot.

The market sizes are (b) (4) 12 gram, 15 gram, 24 gram, and 30 gram (b) (4) tubes.

The MDD is 40 mg/day. (30 g/7days x 1% x 1000mg/g) The IT is (b) (4)%, the QT is (b) (4)%.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable

III. Administrative**A. Reviewer's Signature***Kathy P. Woodland***B. Endorsement Block**

HFD-627/K. Woodland/ *K Woodland 6/24/05*
HFD-627/A. Mueller, PhD/ *A Mueller 6-24-05*
HFD-617/B. Danso, Pharm D., PM/
V:\FIRMSNZ\TAROLTRS&REV\77511.CR1.DOC

C. CC Block

15 pages have been withheld as b4 (CCI/TS) immediately following this page

cc: ANDA 77-511
ANDA DUP 75-511
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K. Woodland/ *K Woodland 6/29/05*
HFD-627/A. Mueller, PhD/ *A Mueller 6-29-05*
HFD-617/B. Danso, Pharm D., PM/6-28-05

V:\FIRMSNZ\TARO\LTRS&REV\77511.CR1.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

#2

ANDA 77-511
FIRST GENERIC

Terbinafine Hydrochloride Cream, 1%

Taro Pharmaceuticals U.S.A., Inc.

Kathy P. Woodland
Division of Chemistry I
Team 5

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III. Administrative.....	8
A. Reviewer's Signature	8
B. Endorsement Block	8
C. CC Block.....	8
Chemistry Assessment	9



#2

Chemistry Review Data Sheet

1. ANDA 77-511
2. REVIEW #:2
3. REVIEW DATE: September 20, 2005
Revised January 30, 2006
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original Submission	December 30, 2004
Acceptable for Filing	January 3, 2005
Amendment (add alternate source of drug substance)	March 9, 2005
Amendment (labeling)	May 25, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment

August 23, 2005

7. NAME & ADDRESS OF APPLICANT:

Name: Taro Pharmaceuticals U.S.A., Inc.
Address: 5 Skyline Drive
Hawthorne, N.Y. 10532
Representative: Kalpana Rao
Telephone: 914-345-9001

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Terbinafine Hydrochloride Cream, 1%

9. LEGAL BASIS FOR SUBMISSION:

- a. The basis of Taro's proposed ANDA for Terbinafine Hydrochloride Cream, 1% is the approved listed drug, Lamisil, NDA 20980, held by Novartis Consumer Health Inc.
b. There is no unexpired exclusivity for Lamisil Cream, 1%. There is one patent #4755534, which will expire on Dec. 30, 2006.

10. PHARMACOL. CATEGORY: Treatment of Athlete's foot.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 10 mg/g (1%)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: ___ Rx ___ x ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___ SPOTS product – Form Completed

___ x ___ Not a SPOTS product

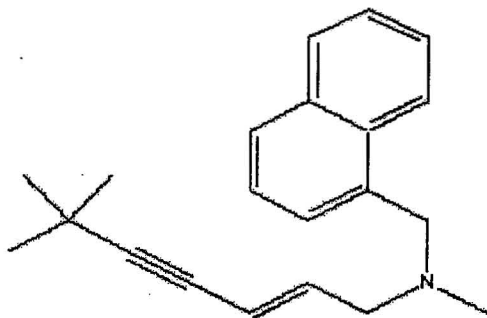
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

TRANS-N-(6,6-DIMETHYL-2-HEPTEN-4-YNYL)-N-METHYL-; Lamisil (free base); Lamosil; 1-Naphthalenemethanamine, N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-, (E)-, monohydrochloride;

Chemistry Review Data Sheet

Molecular Formula: $C_{21}H_{26}ClN$

Molecular Weight: 327.90



HCL

17. RELATED/SUPPORTING DOCUMENTS: None

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate	9/23/05 K. Woodland	
				1	Adequate	1/26/06 K. Woodland	
				4			
				4			
				4			
				4			
				4			
				4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	Not Required		
Labeling	Acceptable	7/13/05	Ruby Wu
Bioequivalence	Acceptable	1/6/06	C. Kim
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:



The Chemistry Review for ANDA 77-511

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This product is a FIRST GENERIC. Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Terbinafine Hydrochloride drug substance is a white to off-white crystalline powder. The drug substance is soluble in methylene chloride and methanol; sparingly soluble in acetone, ethanol, 2-propanol; slightly soluble in water; practically insoluble in toluene.

Drug Product:

The product is

(b) (4)

The MDD is 40 mg/day. (30 g/7days x 1% x 1000mg/g). The IT is (b) (4)%, the QT is (b) (4)%.

B. Description of How the Drug Product is Intended to be Used

The drug product Terbinafine Hydrochloride Cream, 1% is an OTC product used for the treatment of Athlete's Foot (tinea pedis), jock itch (tinea cruris), and body ringworm (tinea corporis) (antifungal).

The treatment is one week for Athlete's Foot between the toes, jock itch, and body ringworm, and two weeks for Athlete's Foot on the bottoms or sides of the foot.

The market sizes are (b) (4), 12 gram, 15 gram, 24 gram, and 30 gram (b) (4) tubes.

The MDD is 40 mg/day. (30 g/7days x 1% x 1000mg/g) The IT is (b) (4)%, the QT is (b) (4)%.



CHEMISTRY REVIEW



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Approvable

III. Administrative

A. Reviewer's Signature

Kathy P. Woodland

B. Endorsement Block

HFD-620/K.Woodland/ *KWoodland 1/30/06*
HFD-620/G.Bykadi, PhD/ *G. Bykadi 1-31-2006*
HFD-617/B. Danso, Pharm D., PM/
V:\FIRMSNZ\TARO\LTRS&REV\77511.CR2.DOC

C. CC Block

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CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 77-511
ANDA DUP 75-511
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K. Woodland/ *K. Woodland 1/30/06*
HFD-627/G. Bykadi, PhD/ *G. Bykadi 1-31-2006*
HFD-617/B. Danso, Pharm D., PM/1-19-06

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TYPE OF LETTER: CMC APPROVABLE

**ANDA 77-511
(FIRST GENERIC)**

Terbinafine Hydrochloride Cream, 1%

Taro Pharmaceuticals U.S.A., Inc.

**Kathy P. Woodland
Division of Chemistry I
Team 5**



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Chemistry Review Data Sheet

1. ANDA 77-511
2. REVIEW #: 3
3. REVIEW DATE: April 30, 2007
Revised June 26, 2007
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original Submission	December 30, 2004
Acceptable for Filing	January 3, 2005
Amendment (add alternate source of drug substance)	March 9, 2005
Amendment (labeling)	May 25, 2005
Amendment	August 23, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment	October 4, 2006
Amendment (Gratuitous amendment)	March 21, 2006
Amendment (Final approval requested)	March 30, 2007
Amendment	June 25, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Taro Pharmaceuticals U.S.A., Inc.
Address: 3 Skyline Drive
Hawthorne, N.Y. 10532



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Kalpana Rao

Telephone: 914-345-9001

Fax 914-593-0078

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Terbinafine Hydrochloride Cream, 1%

9. LEGAL BASIS FOR SUBMISSION:

a. The basis of Taro's proposed ANDA for Terbinafine Hydrochloride Cream, 1% is the approved listed drug, Lamisil, NDA 20980, held by Novartis Consumer Health Inc.

b. There is no unexpired exclusivity for Lamisil Cream, 1%. There is one patent #4755534*PED, which will expire on June 30, 2007.

10. PHARMACOL. CATEGORY: Treatment of Athlete's foot.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 10 mg/g (1%)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: ☐ Rx ☒ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



CHEMISTRY REVIEW

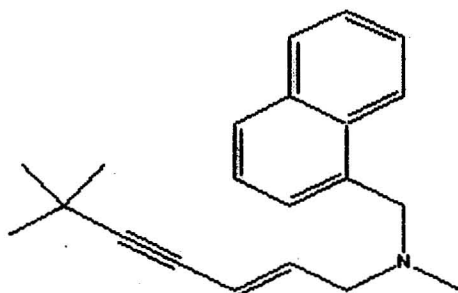


Chemistry Review Data Sheet

TRANS-N-(6,6-DIMETHYL-2-HEPTEN-4-YNYL)-N-METHYL-; Lamisil (free base);
Lamosil; 1-Naphthalenemethanamine, N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-, (E)-,
monohydrochloride;

Molecular Formula: $C_{21}H_{26}ClN$

Molecular Weight: 327.90



HCL

17. RELATED/SUPPORTING DOCUMENTS: None

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate	9/23/05 K. Woodland	
						(b) (4)	WITHDRAWN
				4			
				4			
				4			
				4			
				4			
				4			

*ANDA is a 1A'ed application. No new chemistry related amendments as of June 26, 2007



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	7/6/06	S.Adams
Methods Validation	Not Required		
Labeling	Acceptable	7/13/05	Ruby Wu
Bioequivalence	Acceptable	1/6/06	C. Kim
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:



The Chemistry Review for ANDA 77-511

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This product is a FIRST GENERIC. Approvable. The product was Tentatively approved on March 22, 2006.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Terbinafine Hydrochloride drug substance is a white to off-white crystalline powder. The drug substance is soluble in methylene chloride and methanol; sparingly soluble in acetone, ethanol, 2-propanol; slightly soluble in water; practically insoluble in toluene.

Drug Product:

The product is

(b) (4)

The MDD is 40 mg/day. (30 g/7days x 1% x 1000mg/g). The IT is (b) (4)%, the QT is (b) (4)%.

B. Description of How the Drug Product is Intended to be Used

The drug product Terbinafine Hydrochloride Cream, 1% is an OTC product used for the treatment of Athlete's Foot (tinea pedis), jock itch (tinea cruris), and body ringworm (tinea corporis) (antifungal).

The treatment is one week for Athlete's Foot between the toes, jock itch, and body ringworm, and two weeks for Athlete's Foot on the bottoms or sides of the foot.

The market sizes are (b) (4), 12 gram, 15 gram, 24 gram, and 30 gram (b) (4) tubes.

The MDD is 40 mg/day. (30 g/7days x 1% x 1000mg/g) The IT is (b) (4)%, the QT is (b) (4)%.



CHEMISTRY REVIEW



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Approvable

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kathy P. Woodland
6/27/2007 01:58:44 PM
CHEMIST

Gururaj Bykadi
6/27/2007 02:02:00 PM
CHEMIST

Benjamin Danso
7/2/2007 09:01:13 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-511

BIOEQUIVALENCE REVIEWS

Review of

A Bioequivalence Study

with

Clinical Endpoints

ANDA # 77-511

Taro Pharmaceuticals USA

Terbinafine Hydrochloride Cream,

1%

Carol Kim, Pharm.D.
Clinical Review Team
Submission date reviewed: 12/30/04

Date of Review: 12/28/05
V:\FIRMSnz\taro\ltrs&rev\77511A1204.mor

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Review of A BE Study with Clinical Endpoints for ANDA 77-511

Executive Summary

This double-blind, randomized, single-center, parallel-group study demonstrates that Taro's Terbinafine Hydrochloride Cream, 1%, is safe and bioequivalent to the approved Over the Counter (OTC) product, Lamisil^{AT} 1% Cream, for the treatment of tinea pedis. The FDA statistical review confirms that the 90% Confidence Interval (CI) of the difference in therapeutic cure rates between the test and reference products at the 5 weeks follow-up visit (Visit 3, Week 6) is (-0.108, 0.054), which is within the bioequivalence limits of -0.20 and 0.20. A total of 500 patients with mycologically confirmed tinea pedis were randomized and treated with test, reference, or vehicle. Based on the FDA statistical review, 491 patients were included in the Intent-to-Treat (ITT)¹ population, and 485 were included in the Per Protocol (PP) Population².

I. Recommendation on Approval

The data submitted to ANDA 77-511, using the primary endpoint of therapeutic cure rate at Week 6 (Visit 3, 5 weeks post treatment visit), are adequate to demonstrate bioequivalence of Taro's Terbinafine Hydrochloride Cream, 1%, with the reference listed drug, Novartis' Lamisil^{AT} 1% Cream. Therefore, the test product is recommended for approval.

II. Summary of Clinical Findings

The data presented in this ANDA 77-511 demonstrate that Taro Pharmaceuticals USA, Inc.'s Terbinafine Hydrochloride Cream, 1%, is bioequivalent to the reference listed drug, Lamisil^{AT} (terbinafine hydrochloride) Cream, 1%.

A. Brief Overview of Clinical Program

The study #TRB 0401 was a randomized, double-blind, comparative study of Taro's Terbinafine Hydrochloride Cream, 1%, versus the reference listed drug, Lamisil^{AT} (terbinafine hydrochloride) Cream, 1%, in the treatment of tinea pedis. Five hundred (500) patients with

¹ Included all randomized patients who met inclusion/exclusion criteria, mycologically confirmed tinea pedis, received at least one dose of study medication and completed one post-baseline assessment.

² Included all randomized patients who met inclusion/exclusion criteria, mycologically confirmed with tinea pedis, complied with the minimum treatment course, returned to the study site within the specified window and did not have any protocol violations.

Clinical Review Section

tinea pedis confirmed by fungal culture were randomized in a 2:2:1 ratio to receive the test, reference, or placebo/vehicle cream twice daily for 7 days.

B. Comparative Efficacy

The primary endpoint of this study is a therapeutic cure at the week 6 visit (Visit 3, 5 weeks follow-up after completion of 1 week of treatment). Therapeutic cure was defined by the sponsor as a combination of clinical cure and mycological cure. The sponsor defined a clinical cure as erythema score ≤ 2 and sum of all other symptom scores < 2 at the 6-week visit. Mycological cure was defined by the sponsor based on a negative KOH wet mount for pseudohyphae and a negative culture for tinea pedis species at the 6-week visit (visit 3).

According to the FDA statistical analysis, therapeutic cure rates in the Per Protocol (PP) Population at Visit 3 were 70% in the test group and 72% in the reference group. The 90% CI for the difference in therapeutic cure rates between the two active products was (-0.108, 0.054), which is within the bioequivalence limits of (-0.20 and +0.20).

C. Comparative Safety

The safety data submitted in this ANDA confirms that the test product is not causing any worse adverse events compared to the reference product in the treatment of tinea pedis. A total of 164 adverse events occurred in the study (66 in the test, 58 in the reference and 40 in the vehicle group). The most frequent adverse event reported in the active treatment groups was headache (9/66 Test and 16/58 Reference). In the vehicle group, burning was the most frequently reported adverse event.

Burning (3.7% test, 3.3% reference, and 7.5% vehicle) at the application site was the most frequent skin related adverse event reported in all treatment groups.

Two patients (469 test, 362 vehicle) reported adverse events (hospitalized due to a fracture of the femur and a severe asthma attack) that were considered serious but not related to the study treatment by the investigator.

Clinical Review

I. Introduction and Background

Tinea Pedis is a dermatophytic infection of the feet, characterized by erythema, chronic diffuse desquamation, and /or bulla formation. *T. rubrum* is the most common cause of chronic tinea pedis and *T. mentagrophytes* causes more inflammatory lesions. Once established, the individual becomes a carrier and is more susceptible to recurrences³. The demonstration of hyphae on direct microscopy and isolation of dermatophyte on fungal culture confirm the diagnosis.

³ Habif, Thomas. Clinical Dermatology: A Color Guide to Diagnosis and Therapy (3rd edition, 1996), p. 366.

Clinical Review Section

A. Drug Established Name, Drug Class,

Drug Established Name: Terbinafine Hydrochloride Cream, 1%

Drug Class: Antifungal agent

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Lamisil^{AT} Cream (NDA 20980, OTC), Novartis

Date of approval: 3/9/99

Approved indication(s): Non-prescription topical treatment for athlete's foot (*tinea pedis*), jock itch (*tinea cruris*) and ringworm (*tinea corporis*).

Recommended dosing regimens: For treatment of athlete's foot, apply twice a day for 1 week (between the toes only) or 2 weeks (bottom or sides of the foot). For treatment of jock itch and ringworm, apply once a day for 1 week.

C. Regulatory Background

The following submissions have been reviewed by the OGD for Terbinafine Hydrochloride Cream:

1. INDs, Protocols, and/or Control Documents submitted by Taro

<u>Submission</u>	<u>Submission date</u>	<u>Name of the Product</u>
CD# 04-499	5/25/04	terbinafine hydrochloride

2. INDs, Protocols, and/or Control Documents submitted by other sponsors

<u>Submission</u>	<u>Submission date</u>	<u>Name of the Product/Sponsor</u>
(b) (4)		

3. Previous ANDA submissions for same or related product

none

D. Other Relevant Information

Terbinafine was approved for a prescription use under NDA 20-192 (Lamisil[®] Cream 1%) in 1992 for the treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, or *Trichophyton rubrum*. In 1997, supplemental NDA was approved for the treatment of plantar tinea pedis (moccasin type) due to *Trichophyton mentagrophytes* or *Trichophyton rubrum*. In 1998, Novatis proposed to switch

Clinical Review Section

terbinafine hydrochloride 1% cream from the prescription product to the over the counter product. Novartis initially proposed to [REDACTED] (b) (4) but on March 9, 1999, NDA 20-980 (Lamisil^{AA} Cream 1%) was approved for the non-prescription topical treatment of tinea pedis (athlete's foot), tinea cruris (jock itch) and tinea corporis (ringworm). The Lamisil[®] interdigital and plantar tinea pedis indications were combined into an "athlete's foot" indication for OTC product and the directions were split with regard to duration of treatment and anatomic location of the disease on the foot.

II. Description of Clinical Data and Sources

Study Centers/Investigators: The study was performed by a single investigator.

Site	Investigator	Address	Number of patients eligible for randomization
1	Howard Yanofsky, M.D.	5885 Cote Des Neiges #609, Montreal, Quebec	535

Study Period: September 4, 2004 to November 18, 2004

Enrollment: A total of 968 patients were initially screened and 433 patients failed to meet the randomization criteria. Of 535 patients eligible for randomization, thirty five (35) patients were discontinued after randomization due to negative baseline culture specimen (33 patients) and negative baseline KOH result (2 patients).

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: ANDA 75-711, Vol. 1.1-1.6, submitted on 12/30/04

Study Amendment: none

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report:

The DSI inspection was not requested for this study due to previous satisfactory inspection history on the same clinical site (ANDAs 75-883, review dated 2/26/03 and 75-953, review dated 1/20/04).

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor declared that the study was conducted under the guiding principals of the Declaration of Helsinki. The sponsor's original protocol and consent forms were reviewed and approved by the Ethics Review Committee prior to initiation of the study.

Clinical Review Section

Reviewer's Comment: *The sponsor's study appears to be in compliance with the accepted ethical standards.*

D. Evaluation of Financial Disclosure: The sponsor submitted a signed financial disclosure document certifying that the principal investigator (Dr. Yanofsky) has not entered into any financial arrangement with the sponsor that could be affected by the outcome of the study and declared that he has not received significant payment of other sorts as defined in 21 CFR 312.63(f).

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The sponsor's study demonstrates the bioequivalence of the test product with the reference product.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #TRB 0401) was reviewed to determine bioequivalence of the test product and the reference product. The primary endpoint of this product is a therapeutic cure (both clinical and mycological cure) at the week 6 visit (5 weeks post treatment). The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

Protocol Review (TRB 0401):

1. The sponsor's protocol was amended two times prior to this submission.
2. Taro submitted the original protocol on May 25, 2004 (CD #04-499) and the OGD provided the following comments related to the primary endpoint analysis:
 - Patients should apply the study drug twice daily for 7 days and should be evaluated for therapeutic cure at study week 6 (5 weeks after the end of treatment).
 - To be included in the study, patients should have clinical diagnosis of tinea pedis with lesions localized to the interdigital spaces or predominantly interdigital but may extend to other areas of the foot; clinical diagnosis of tinea pedis confirmed by both positive KOH and culture results at baseline; and total sum of the scores of the clinical signs and symptoms of the target lesion should be at least 6, including a minimum score of at least 2 for erythema and a minimum score of 2 for either scaling or pruritis at the baseline target test site.
 - The recommended primary endpoint of this product is a therapeutic cure, which is both clinical and mycological cure. Clinical cure is defined as a total score of ≤ 2 for erythema and <2 for all other signs and symptoms. Mycological cure is defined as a negative KOH and a negative fungal culture results.

Clinical Review Section

- A Physician's Global Assessment may be used as a secondary endpoint.
- 3. After receiving the FDA comments dated August 18, 2004, the sponsor's protocol was revised (Amendment 1, 8/26/04) to incorporate the following changes:
 - Entry criteria: only KOH positive patients were enrolled and randomized to treatment. Patients must also have moderate erythema and moderate scaling or pruritus at baseline to meet entry criteria. Two symptoms, maceration and exudation, were added for clinical evaluation.
 - Modified exclusion criteria to include peripheral vascular disease, neuropathy of the feet, history of atopic dermatitis, contact dermatitis, or psoriasis involving the feet, onychomycosis, and previous enrollment in the study.
 - The definition of cure was evaluated only at the 6-week visit, eliminating the 4-week visit. The proposed primary endpoint was the therapeutic cure at the 6-week visit.
 - Patients were permitted to miss 3 doses in the 7-day period or use an additional 3 doses to be considered evaluable.
 - Reduced the wash-out period of topical corticosteroid or antifungal therapy to 2 weeks (instead of 1 month).
- 4. The first patient was enrolled on September 4, 2004.
- 5. Protocol Amendment #2 was issued on 9/22/04. This amendment changed the visit window for the 1-week return visit from +1 day to +3 days and made minor administrative changes into the protocol.

Sponsor's protocol#: TRB 0401

Title: A 3-Way, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Therapeutic Equivalence of Terbinafine Hydrochloride Cream, 1%, Manufactured by Taro Pharmaceuticals Inc. and Lamisil[®] AT Cream Manufactured by Novartis in the Treatment of Clinically Diagnosed and Mycologically Confirmed Interdigital Tinea Pedis

Objective: The primary purpose of this study was to demonstrate comparable safety and efficacy of Taro Pharmaceuticals Inc.'s terbinafine hydrochloride cream 1% (test product) and Lamisil[®] AT Cream (reference listed drug) in the treatment of interdigital tinea pedis, and to show the superiority of the active treatments over that of the placebo (vehicle).

Study Design: This was a randomized, double-blind, parallel-group, placebo-controlled study design comparing the following products:

1. Test: Terbinafine Hydrochloride Cream, 1%, Taro Pharmaceuticals USA Inc., applied topically twice daily for 7 days; lot # (L) S182-54787
2. Reference: Lamisil[®] AT Cream (terbinafine hydrochloride), 1%, Novartis, applied topically twice daily for 7 days; lot #(L)326706
3. Vehicle/Placebo: Taro's vehicle, applied topically twice daily for 7 days; lot #S182-54786

Clinical Review Section

Blinding:

The study medications were supplied by the sponsor in individual patient kits, each containing one tube of study drug (Taro, Novartis, or vehicle). The Novartis product was used in its commercial form covered by an opaque label and a study label. Tubes were placed in identical cartons that were labeled as described below. Each tube and carton (patient kit) was covered with identical labels (in English and French) with the following information: protocol number, treatment identification number (treatment ID), reference to directions for use, a note that drug is for investigational use only, and storage conditions.

Neither the patient nor the investigator knew the origin of the terbinafine hydrochloride cream 1% in the patient kit. Blinding and labeling were performed by Taro. The randomization code was retained by the Clinical Pharmacy Associate at Taro.

In the event that it was necessary to break the blind (e.g., for patient safety), the investigator was to contact the study manager who would obtain the necessary information.

Study Population: Patients at least 18 years of age or older with clinical signs and symptoms of tinea pedis. Patients who met the following criteria were eligible for the study:

Inclusion Criteria

1. At least 18 years of age; no upper age limit was established.
2. Males and non-pregnant, non-nursing female patients.
3. Clinical diagnosis of interdigital tinea pedis provisionally confirmed by presence of segmented fungal hyphae on KOH mount.
4. A minimum severity score of 2 for erythema and 2 for either scaling or pruritus on the same target lesion, and a total sum of the scores of the clinical signs and symptoms of the target lesion of at least 6.
5. Positive culture for *T. rubrum*, *T. mentagrophytes*, *Epidermophyton floccosum*, or other causative dermatophytes.
6. Signed informed consent after the study had been fully explained and before any procedures dictated by the protocol were performed.
7. Women of childbearing potential had to have a negative urine pregnancy test result prior to entry into the study and had to agree to use a medically accepted form of birth control.
8. Patients able to comply with all requirements of the protocol.

Exclusion Criteria

1. Received systemic corticosteroid, anti-fungal, or other anti-infective therapy within one month prior to enrollment.
2. Received topical corticosteroid or anti-fungal therapy to the feet within 2 weeks prior to enrollment.
3. Received immunosuppressive medication or radiation therapy within 3 months prior to enrollment.
4. Concomitant yeast infection or bacterial infection that is systemic or localized to the foot.

Clinical Review Section

5. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
6. Concurrent onychomycosis of the toenails of the foot.
7. Signs of systemic fungal disease.
8. Pregnancy or breast-feeding.
9. Uncontrolled diabetes mellitus, peripheral vascular disease, neuropathy of the feet, or any significant medical conditions likely to compromise participation of the study or place the patient at risk.
10. History of atopic dermatitis, contact dermatitis, or psoriasis involving the feet.
11. Known allergy or sensitivity to any of the study medications or inactive ingredients.
12. Previously enrolled in the study.
13. Participated in another clinical study within the previous month.
14. Delayed exclusion if the culture taken at baseline proves to be negative for dermatophyte or shows evidence of a significant concomitant yeast or bacterial infection.

Criteria for discontinuation of study:

Patients were discontinued from the study after randomization for any of the following reasons:

- Patient's decision to leave the study for any reason.
- Development of an intercurrent condition or complication which could have affected the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the investigator.
- Pregnancy.
- Ingestion or topical application of any interdicted medication (oral antibiotics or antifungal agents, or topical application of any other medications to the affected areas for the entire time of the study).
- Failure to comply with the protocol.

Use of any of the following medications prior to randomization (enrollment) was considered non-eligible and use during the study was considered a protocol violation resulting in discontinuation from the study.

- Systemic corticosteroid, antifungal, or other anti-infective therapy within 1 month prior to entry into the study.
- Topical corticosteroid or anti-fungal therapy to the feet within 2 weeks prior to entry into the study.
- Immunosuppressive medication or radiation therapy within 3 months of entry into the study.
- Participation in another clinical study within the previous month.
- Ingestion or topical application of any interdicted medication.
- Any oral antibiotics or antifungal agents, or application of any other medications to the affected areas for entire time of the study.

Treatment Compliance

Treatment compliance (>75% and <125% of scheduled doses) was encouraged by

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instructing the patient in use of the daily diary. Compliance with the protocol requirements was assessed by the principal investigator at each visit by questioning the patient regarding the study drug and other medication use.

Based on the FDA comments issued on 8/18/04, the final protocol allowed patients to miss 3 doses in the 7 day period, or use an additional 3 doses to be considered treatment compliance.

Reviewer's Comments: *No patient in the sponsor's per protocol population received an additional dose in the 7 day study period. One patient (146) who received the study drug 4 times a day was excluded from the sponsor's per protocol population due to protocol violation.*

Procedures/Observations, and safety measures:

Visit 1(Day 1); Enrollment and Treatment day

The medical history and foot assessments were completed. Patients underwent laboratory testing. Female patients with childbearing potential performed urine pregnancy tests. A 10% KOH smear was taken from an area of active lesion (study foot).

Mycological and Clinical assessments were performed as follows:

1) Mycological Assessment

- a. 10% potassium hydroxide (KOH) smear was examined microscopically for evidence of fungus.
- b. Mycological cultures were obtained for *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum* or other causative dermatophyte (the majority of patients should have cultures positive for *T. rubrum*). Other organisms were identified but the culture results were listed as "negative" for the purpose of the study.

2) Clinical Assessment

During the examination of the foot, the signs and symptoms were graded on a 4-point scale. Patients recorded the severity of symptoms of itching and burning and the investigator evaluated the severity of erythema, fissuring, maceration, vesiculation, desquamation (scaling), and exudation using the same 4-point scale as follows:

<u>Investigator's evaluation</u>	<u>Patient's evaluation</u>	<u>Scale</u>
• erythema	Itching	0=none
• scaling (desquamation)	Burning	1=mild
• fissuring		2=moderate
• maceration		3=Severe
• vesiculation		
• exudation		

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Patients were given a package of study medication and instructed to follow all instructions provided.

Visit 2 (Day 7 +3 days); End of treatment (Week 1) visit

One week (+ 3 days) after initiating of study treatment, patients were instructed to return the study medication and diary. Patients were questioned concerning possible adverse events and compliance with the protocol. Any adverse events or changes to concomitant medications were documented. Women of child-bearing potential repeated urine pregnancy tests.

Visit 3 (Day 42 +/-3 days); follow-up Week 6 visit, Primary Endpoint Visit

Five weeks after completion of 1 week study treatment, patients repeated clinical and mycological assessments on the study foot. Clinical signs and symptoms of tinea pedis were recorded, and specimens of the lesions were obtained for evaluation by 10% potassium hydroxide smear and by mycological culture. These assessments were repeated using the same scale as proposed at Visit 1.

Endpoints:

The primary endpoint is a therapeutic (both clinical and mycological) cure.

Definitions:

- Clinical Cure: an erythema score ≤ 2 with the sum of all other symptom scores < 2 at the 6-week visit.
- Mycological Cure: a negative KOH smear and a negative mycological culture at the 6-week visit. If the KOH was not available, the cure was based solely on the mycological culture.
- Therapeutic cure: Both a clinical and mycological cure.

Patients who were discontinued early from the study due to protocol violations or missed the 6-week visit were excluded from the per protocol (PP) analysis and were classified as treatment failures in the intent-to-treat (ITT) population analysis.

Reviewer's Comments: *Patients dropped due to protocol violations should be excluded from the PP population analysis but included in the ITT population analysis using the LOCF method.*

Statistical analysis plan

Primary Endpoint: The primary endpoint is the therapeutic cure at the 6-week visit. Secondary endpoint evaluation was performed on clinical and mycological cure rates at the 6-week visit.

Sample Size: At least five hundred patients were proposed to allow 200 patients per active treatment group and 100 patients in the vehicle/placebo group to complete the study. This

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sample size was proposed based on the sponsor's estimated calculation of cure rate of 66% for the Taro and the RLD groups.

Analysis: For the bioequivalence analysis, the 90% confidence interval was constructed for the difference in therapeutic cure rates between the test and the reference products at the 6-week visit. If the 90% Wald confidence limits, using Yate's continuity correction, were within -0.20 and +0.20, the test was considered therapeutically equivalent to the RLD. Superiority of each active treatment over the placebo was evaluated in the ITT population at the 6-week visit by independent, two-sided, $\alpha=0.05$, continuity-corrected Z-tests on the differences between active treatment and placebo therapeutic cure rates.

Demographic characteristics were summarized with descriptive statistics to assess the comparability of the treatment groups.

Study Conduct

Discussion of ITT and PP populations:

Two patient populations were defined by the sponsor as follows:

Intent-to-treat (ITT): all patients who had mycologically confirmed tinea pedis and received at least one dose of study medication. For the ITT population analysis, patients missing the 6-week visit were classified as treatment failures.

Reviewer's Comment: *Patients with no post baseline data should be excluded from both ITT and PP populations.*

Per-protocol (PP): Patients who had mycologically confirmed tinea pedis (positive mycological culture at the baseline visit), had clinical and mycological data at the 6-week visit, had completed the visit 3 within the visit window of 39-45 days, and had not violated protocol. Any patient missing either follow-up visit because of early declared treatment failure was included as a clinical, mycological, and therapeutic failure.

Retention of Reserve Samples:

The sponsor's protocol proposes to ship the blinded and labeled study drug to the investigator who then was instructed to remove samples in a random fashion and ship them to an independent 3rd party facility for storage.

Reviewer's Comment: *The detailed explanation of retention sample procedure was not provided in the study report.*

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Demographics

Of the 500 treated patients, 351 (70%) were Caucasian, 39 (8%) were Black, 87 (17%) were Hispanic, and 23 (5%) were classified as "other". Baseline demographics, age, and race in the ITT population were similar in all treatment groups. The mean age was 38.3 (18-75), 40.2 (18-80) and 38.8 (19-77) years for the test, reference and vehicle groups, respectively. The demographic characteristics for all treated patients are tabulated by the sponsor in Table I.

Table I: Demographic Characteristics for 500 treated patients (per sponsor)

Characteristic		TARO (N=199)	RLD (N=199)	Vehicle (N=102)	Total (N=500)
Race	Caucasian	144 (72%)	135 (68%)	72 (71%)	351 (70%)
	Black	12 (6%)	16 (8%)	11 (11%)	39 (8%)
	Hispanic	30 (15%)	40 (20%)	17 (17%)	87 (17%)
	Other	13 (7%)	8 (4%)	2 (2%)	23 (5%)
Age (years)	Mean (Std)	38.3 (12.2)	40.2 (12.1)	38.8 (11.9)	39.2 (12.1)
	Min - Max	18 - 75	18 - 80	19-77	18-80
Gender	Male	149 (75%)	164 (82%)	75 (74%)	388 (78%)
	Female	50 (25%)	35 (18%)	27 (26%)	112 (22%)

Baseline disease severity

The sponsor tabulated mean severity scores for each sign and symptom of tinea pedis at baseline for the ITT population in Table II. The mean severity scores were similar in all treatment groups for the ITT population. The sponsor did not provide baseline disease severity scores for the PP population.

Table II: Mean Severity Scores for Signs and Symptoms of T. Pedis at Baseline for Treatment Groups: ITT population (per sponsor)

TREATMENT	N	Fissuring		Erythema		Maceration		Vesiculation		Desquamation		Exudation		Pruritus		Burning/ Stinging		Total*	
		mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
TARO	199	0.56	0.55	2.22	0.41	0.35	0.62	0.00	0.00	2.20	0.53	0.01	0.10	2.51	0.59	0.88	0.87	8.72	1.99
RLD	199	0.61	0.65	2.23	0.42	0.34	0.59	0.00	0.00	2.25	0.56	0.00	0.00	2.44	0.64	0.75	0.84	8.63	1.74
VEHICLE	102	0.50	0.54	2.25	0.43	0.37	0.64	0.02	0.14	2.17	0.51	0.01	0.10	2.46	0.64	0.80	0.86	8.58	1.86
For difference between treatment groups p=		0.29		0.84		0.91		0.02		0.37		0.37		0.57		0.31		0.79	

* Sum of individual sign/symptom scores for each patient

Reviewer's Comment: Except for the sign of vesiculation, there was no statistically significant difference between treatment groups for individual mean baseline clinical sign and symptom scores or total signs and symptoms scores at baseline in the sponsor's defined ITT population.

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Baseline Fungal Culture

The majority of patients had the baseline fungal culture positive for *Trichophyton rubrum* (81.6%) in the sponsor's ITT population. The other dermatophytes isolated were *T. Mentagrophytes* (10.8%) and *Epidermophyton Floccosum* (7%). Three patients (0.6%) in the test group had baseline fungal culture positive for *T. raubitschekii* and *T. violaceum*. According to the sponsor's analysis, the percentage of patients with baseline fungal culture positive for *Trichophyton rubrum* was comparable in all treatment groups ($p=0.13$).

Reviewer's Comments: *Three patients (patient ID # 70, 271, and 607) in the test group had baseline fungal culture positive for T. raubitschekii and T. violaceum and were included in the PP population analysis by the sponsor.*

T. raubitschekii is a dermatophyte that belongs to the T. rubrum complex and is more commonly associated with tinea corporis. T. violaceum is a dermatophyte known to be associated with tinea capitis. Since these microorganism species were identified with clinical symptoms of tinea pedis and the majority of infections were caused by T. rubrum in this study, this reviewer agrees with the sponsor's decision to include these patients in the PP population analysis.

Results

Of 968 patients initially screened for the study, 433 patients were considered as screening failures (negative KOH, does not meet inclusion/exclusion criteria) at baseline. Of 535 patients randomized, 35 patients were excluded at baseline due to negative baseline KOH or culture results. A total of 500 patients (199 test, 199 reference, 102 vehicle) were treated and included in the ITT population by the sponsor.

The distribution of patients per treatment arm for each analysis population is shown in Table III. Table IV shows the sponsor's efficacy outcome analysis for the per protocol (PP) population.

Table III: Patient Disposition (per sponsor)

	TARO	RLD	VEHICLE	ALL
Safety Population	214	214	107	535
All randomized patients				
Exclusions:				
Negative KOH	1	0	1	2
Negative culture	14	15	4	33
Intent-to-Treat Population	199	199	102	500
(all eligible randomized patients)				
Exclusions:				
Missing visits 2 and 3	1	1	2	4
Missing visit 3	3	1	0	4
Other protocol violations	4	2	1	7
Outside window for visit 3	0	0	0	0
Per Protocol Population	191	195	99	485
Visit 3: 39-45 days				