CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-790

Name: Ciclopirox Olamine Cream USP, 0.77%

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

Approval Date: April 12, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

APPROVAL LETTER

ANDA 76-790

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

APR 12 2004

APR 12 2005

4/15/05

Dear Madam:

This is in reference to your abbreviated new drug application dated June 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ciclopirox Olamine Cream USP, 0.77%.

Reference is also made to your amendments dated March 12, June 2, and October 21, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ciclopirox Olamine Cream USP, 0.77% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Loprox® Topical Cream of Medicis Pharmaceutical Corp.).

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

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(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

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 (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

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

4/12/05

cc: ANDA 76-790
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-629/G.Kang/GK 4/8/05
HFD-623/J.Fan/ 4/9/05
HFD-617/T.Vu/
HFD-613/B.Weitzman/ 4/11/05
HFD-613/J.Grace/

Received 4/12/05

V:\FIRMSNZ\TARO\LTRS&REV\76790.ap.DOC
F/T by

APPROVAL

CKuo for Bob West 4/12/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

LABELING

FRONT

APPROVED
APR 12 2005

PK-0000-0
000

Ciclopirox Olamine Cream USP, 0.77%

Rx Only

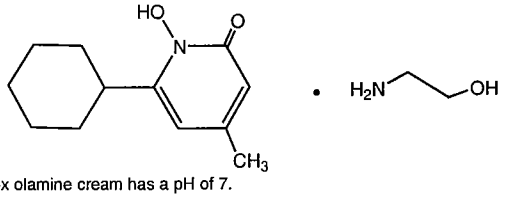
FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

DESCRIPTION
Ciclopirox Olamine Cream USP, 0.77% is for topical use.

Each gram of Ciclopirox Olamine Cream USP contains 7.70 mg of ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of cetyl alcohol, cocamide DEA, lactic acid, mineral oil, myristyl alcohol, octyldodecanol, polysorbate 60, purified water, sorbitan monostearate, stearyl alcohol, and benzyl alcohol (1%) as preservative.

Ciclopirox olamine cream contains a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt.

The CAS Registry Number is 41621-49-2. The chemical structure is:



Ciclopirox olamine cream has a pH of 7.

CLINICAL PHARMACOLOGY
Ciclopirox is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur*. Ciclopirox exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermorphyton floccosum*, *Microsporum canis*, and *Candida albicans*.

Pharmacokinetic studies in men with tagged ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm^2 on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.

Penetration studies in human cadaverous skin from the back, with Ciclopirox Olamine Cream USP, 0.77% with tagged ciclopirox showed the presence of 0.8 to 1.6% of the dose in the stratum corneum 1.5 to 6 hours after application. The levels in the dermis were still 10 to 15 times above the minimum inhibitory concentrations.

Autoradiographic studies with human cadaverous skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and Photo-Draize study conducted in a total of 142 healthy male subjects showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photo-contact sensitization due to Ciclopirox Olamine Cream USP, 0.77%.

INDICATIONS AND USAGE
Ciclopirox olamine cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*; candidiasis (moniliasis) due to *Candida albicans*; and tinea (pityriasis) versicolor due to *Malassezia furfur*.

CONTRAINDICATIONS
Ciclopirox olamine cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS
Ciclopirox olamine cream is not for ophthalmic use.

Keep out of reach of children.

PRECAUTIONS
If a reaction suggesting sensitivity or chemical irritation should occur with the use of ciclopirox olamine cream, treatment should be discontinued and appropriate therapy

instituted.

Information for Patients:
The patient should be told to:
1. Use the medication for the full treatment time even though symptoms may have improved and notify the physician if there is no improvement after four weeks.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
A carcinogenicity study in female mice dosed cutaneously twice per week for 50 weeks followed by a 6-month drug-free observation period prior to necropsy revealed no evidence of tumors at the application site.

The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olamine: studies to evaluate gene mutation in the Ames *Salmonella*/Mammalian Microsome Assay (negative) and Yeast Saccharomyces Cerevisiae Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Lethal Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative).

The following battery of *in vitro* genotoxicity tests were conducted with ciclopirox: a chromosome aberration assay in V79 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assay in the HGPRT – test with V79 Chinese Hamster Cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA Synthesis Assay in A549 Human Cells (negative)). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cyctogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

Pregnancy Category B:
Reproduction studies have been performed in the mouse, rat, rabbit, and monkey (via various routes of administration) at doses 10 times or more the topical human dose and have revealed no significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ciclopirox Olamine Cream USP, 0.77% is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

ADVERSE REACTIONS
In all controlled clinical studies with 514 patients using ciclopirox olamine cream and in 296 patients using the vehicle cream, the incidence of adverse reactions was low. This included pruritus at the site of application in one patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in one patient and worsening of the clinical signs and symptoms in another patient using the vehicle cream.

DOSAGE AND ADMINISTRATION
Gently massage Ciclopirox Olamine Cream USP, 0.77% into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of treatment with ciclopirox olamine cream, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

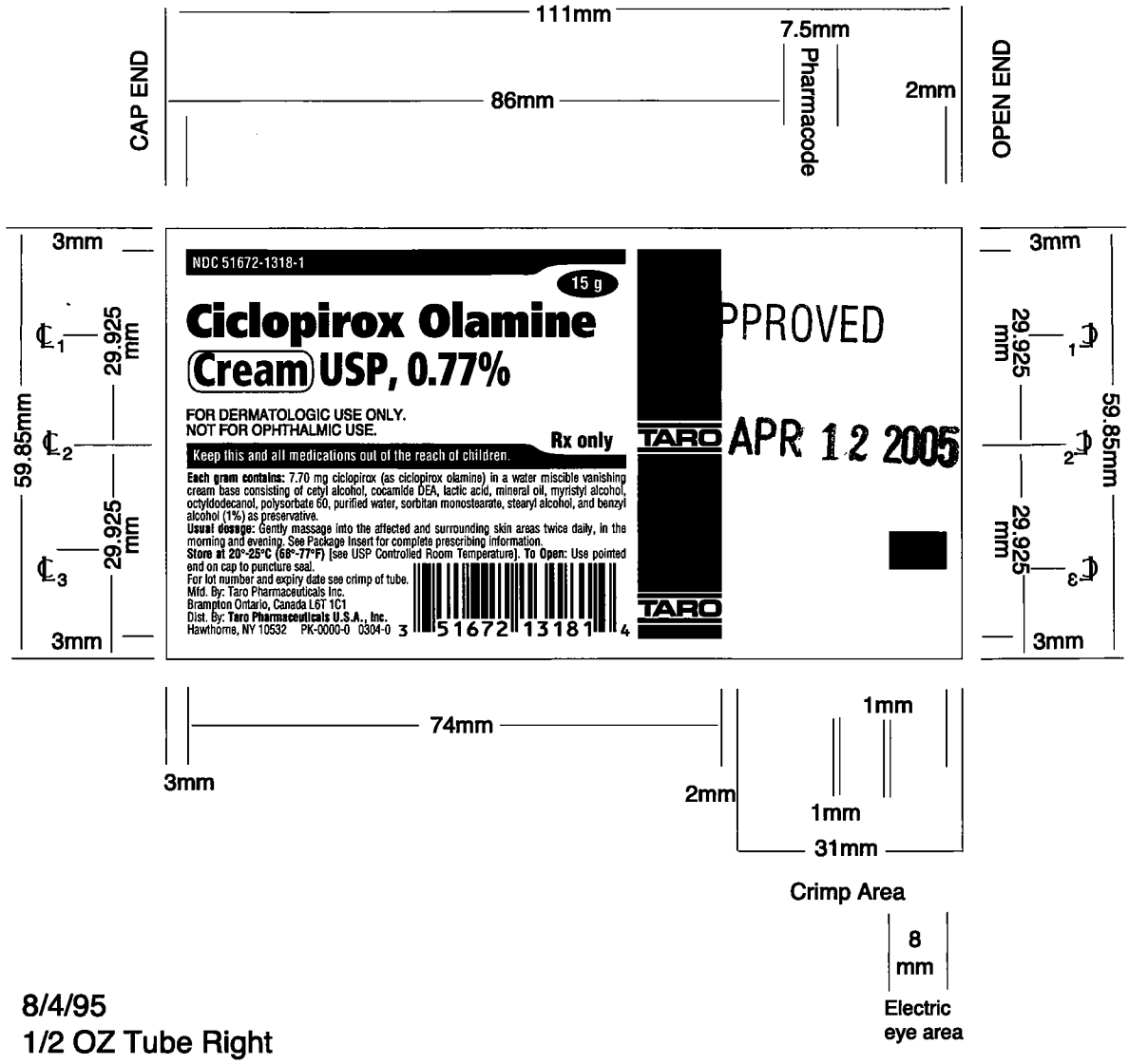
HOW SUPPLIED
Ciclopirox Olamine Cream USP, 0.77% is supplied in 15 g, 30 g and 90 g tubes.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

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

Issued: March 2004

PK-0000-0 0304-0



8/4/95
1/2 OZ Tube Right

8/4/95
1 OZ Tube Right

APPROVED
APR 12 2005

CAP END

165mm

140mm

7.5mm

Pharmacode

2mm

OPEN END

3mm

3mm

NDC 51672-1318-8

90 g

Ciclopirox Olamine Cream USP, 0.77%

49.875 mm

99.75mm

49.875 mm

FOR DERMATOLOGIC USE ONLY.
NOT FOR OPHTHALMIC USE.

Rx only

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

Each gram contains: 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of cetyl alcohol, cocamide DEA, lactic acid, mineral oil, myristyl alcohol, octyldodecanol, polysorbate 60, purified water, sorbitan monostearate, stearyl alcohol, and benzyl alcohol (1%) as preservative.

Usual dosage: Gently massage into the affected and surrounding skin areas twice daily, in the morning and evening. See Package Insert for complete prescribing information.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

To Open: Use pointed end on cap to puncture seal.
For lot number and expiry date see crimp of tube.

Mfd. By: Taro Pharmaceuticals Inc.
Brampton Ontario, Canada L6T 1C1
Dist. By: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
PK-0000-0 0304-0

3 51672 13188 3

TARO

TARO

49.875 mm

99.75mm

49.875 mm

3mm

3mm

1mm

102mm

3mm

2mm /mm 2mm

1mm

47mm
Crimp Area

2mm

8
mm

Electric
eye area

JUNE 29, 2000
85 g Tube Right

Each gram contains: 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of cetyl alcohol, cocamide DEA, lactic acid, mineral oil, myristyl alcohol, octyldodecanol, polysorbate 60, purified water, sorbitan monostearate, stearyl alcohol, and benzyl alcohol (1%) as preservative.
Usual dosage: Gently massage into the affected and surrounding skin areas twice daily, in the morning and evening.
See Package Insert for complete prescribing information.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
For lot number and expiry date see flap of carton and/or crimp of tube.

NDC 51672-1318-1

15 g

Ciclopirox Olamine Cream USP, 0.77%

FOR DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC USE.

Rx only

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

Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.

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

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

3 51672 13181 4

TARO

T 24

PK-0000-0
0304-0
M00

NDC 51672-1318-1

15 g

Ciclopirox Olamine Cream USP, 0.77%

FOR DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC USE.

Rx only

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

TARO

Ciclopirox Olamine Cream USP, 0.77%
NDC 51672-1318-1
15 g

APPROVED
APR 12 2005

Each gram contains: 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of cetyl alcohol, cocamide DEA, lactic acid, mineral oil, myristyl alcohol, octyldodecanol, polysorbate 60, purified water, sorbitan monostearate, stearyl alcohol, and benzyl alcohol (1%) as preservative.
Usual dosage: Gently massage into the affected and surrounding skin areas twice daily, in the morning and evening. See Package Insert for complete prescribing information.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
For lot number and expiry date see flap of carton and/or crimp of tube.

NDC 51672-1318-2

30 g

Ciclopirox Olamine Cream USP, 0.77%

FOR DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC USE.

Rx only

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

Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.

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

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

3 51672 13182 1

NDC 51672-1318-2

30 g

Ciclopirox Olamine Cream USP, 0.77%

FOR DERMATOLOGIC USE ONLY . NOT FOR OPHTHALMIC USE.

Rx only

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

TARO

T 17

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APPROVED
APR 12 2005

Each gram contains: 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of cetyl alcohol, cocamide DEA, lactic acid, mineral oil, myristyl alcohol, octyldodecanol, polysorbate 60, purified water, sorbitan monostearate, stearyl alcohol, and benzyl alcohol (1%) as preservative.
Usual dosage: Gently massage into the affected and surrounding skin areas twice daily, in the morning and evening. See Package Insert for complete prescribing information.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
For lot number and expiry date see flap of carton and/or crimp of tube.

NDC 51672-1318-8

90 g

Ciclopirox Olamine Cream USP, 0.77%

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

Rx only

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

Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.

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

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

3 51672 13188 3

TARO

T 111

M00
0-4030-0
PK-0000-0

APPROVED
APR 12 2005

NDC 51672-1318-8

90 g

Ciclopirox Olamine Cream USP, 0.77%

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

Rx only

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

TARO

Ciclopirox Olamine Cream USP, 0.77%

NDC 51672-1318-8

90 g

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

LABELING REVIEWS

2.1

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-790

Date of Submission: June 30, 2003 and February 17, 2004 (Amendment)

Applicant's Name: Taro Pharmaceuticals

Established Name: Ciclopirox Olamine Cream USP, 0.77%

Labeling Deficiencies:

1. **GENERAL COMMENTS [ALL LABELING]**

   a. Delete "_____" following the established name "Ciclopirox Olamine Cream USP, 0.77%"

   b. Because your stability studies are conducted at 25 ± 2°C, 60% ± 5% RH, revise your storage temperature to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]".

2. **CONTAINER** (15 g, 30 g, 90 g)

3. **CARTON** (15 g, 30 g, 90 g)

   See GENERAL COMMENTS

4. **INSERT**

   See GENERAL COMMENTS

Please revise your labels and labeling, as instructed above, and submit 12 final printed copies for approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
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	
Does USP have labeling recommendations? If any, does ANDA meet them?			
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.		X	
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.		X	

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. **MODEL LABELING**

This review was base on the labeling for Loprox by Medicus (NDA 18-748/S-010): Approved March 26, 2003. This supplement provides for the following revisions:

- The declared strength is revised from "1.0%" to "0.77%"
- The established name is revised from "ciclopirox olamine" to "ciclopirox"
- The active ingredient is identified as "ciclopirox (as ciclopirox olamine)"

Please note, that for the "cream" ciclopirox olamine should be used until the USP monograph is changed to the designation "Ciclopirox" per the supplemental approval letter for NDA 19-824/S-009 (Lotion) which states that "all references in the package insert to LOPROX cream "ciclopirox" should be 'ciclopirox olamine" until the USP mongraph is changed to the designation: Ciclopirox. Also, this information has been confirmed by Frank Cross, PM.

2. **LABELING ISSUES:**

- Taro withdrew the ——— from their application. Taro submitted revised Insert labeling omitted the ——— as of February 17, 2004 submission.

3. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
[Vol. A1.4, pg. 1778]

4. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 18-748

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE			There is no unexpired patent for this product.		NONE

Exclusivity-Data – NDA 18-748

Code	Reference	Expiration	Labeling Impact
NONE	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	NONE

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: Preserve in collapsible tubes, at controlled room temperature.
- RLD: Store at 15°-30°C (59° - 86°F).
- ANDA: Store at [redacted]

Asked the firm to revise their storage temperature to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]", because their stability studies are conducted at 25 ± 2°C, 60% ± 5% RH.

6. **DISPENSING STATEMENT COMPARISON**

- USP: None
- RLD: None
- ANDA: None

7. **PACKAGE CONFIGURATION**

- RLD: Packaged in 15 gram, 30 gram, and 90 gram tubes.
- ANDA: 15 gram, 30 gram and 90 gram package sizes of Ciclopirox Cream USP, 0.77% are packaged in [redacted] aluminum closed end tubes with white — caps with piercing tips.

8. **CONTAINER/CLOSURE**

Packaged in Sealed, white, [redacted] aluminum tubes with white [redacted] caps with piercing tips.
[Vol.1.4, page 2031]

9. **FINISHED DOSAGE FORM**

- RLD: A white odorless cream
- ANDA: Smooth, white cream

[Vol. 1.4 pages. 2125 - 2126]

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario, Canada, L6T 1C1 [Vol. 1.4, page 1894]

Date of Review: **Date of Submission:** JUNE 30, 2003 (Feb. 17, 2004 Amendment)

Primary Reviewer: B. Weitzman B. Weitzman **Date:** 3/03/2004

Team Leader: **Date:** 3/4/04

cc: ANDA 76-790
DUP/DIVISION FILE
HFD-613/Bweitzman/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\76790na1.I
Review

APPROVAL SUMMARY

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

ANDA Number: 76-790

Date of Submission: March 12, 2004

Applicant's Name: Taro Pharmaceuticals

Established Name: Ciclopirox Olamine Cream USP, 0.77%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: (15 g, 30 g and 90 g) – Satisfactory in FPL as of March 12, 2004 submission. [Revised 03/04; Code # PK-0000-0 0304-0]
- Carton Labeling: (15 g, 30 g, and 90 g) – Satisfactory in FPL as of March 12, 2004 submission. [Revised 03/04; Code # PK-0000-0 0304-0 M00]
- Professional Package Insert Labeling: Satisfactory in FPL as of March 12, 2004 submission. [Revised 03/04; Code # PK-0000-0 0304-0]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Loprox Cream, 0.77%
- NDA Number: 19-824
- NDA Drug Name: Ciclopirox Olamine Cream USP, 0.77%
- NDA Firm: Medicus
- Date of Approval of NDA Insert: Supplement S-010: Approved March 26, 2003
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 18-748

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE			There are no unexpired patents for this product in the Orange Book database		NONE

Exclusivity-Data – NDA 18-748

Code	Reference	Expiration	Labeling Impact
NONE	There are no unexpired patents for this product in the Orange Book database	NA	NONE

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
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	
Does USP have labeling recommendations? If any, does ANDA meet them?			
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.		X	
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.		X	

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. **MODEL LABELING**

This review was base on the labeling for Loprox by Medicus (NDA 18-748/S-010): Approved March 26, 2003. This supplement provides for the following revisions:

- The declared strength is revised from "1.0%" to "0.77%"
- The established name is revised from "ciclopirox olamine" to "ciclopirox"
- The active ingredient is identified as "ciclopirox (as ciclopirox olamine)"

Please note, that for the "cream" ciclopirox olamine should be used until the USP monograph is changed to the designation "Ciclopirox" per the supplemental approval letter for NDA 19-824/S-009 (Lotion) which states that "all references in the package insert to LOPROX cream "ciclopirox" should be 'ciclopirox olamine" until the USP mongraph is changed to the designation: Ciclopirox. Also, this information has been confirmed by Frank Cross, PM.

2. **LABELING ISSUES:**

- Taro withdrew the ——— from their application. Taro submitted revised Insert labeling omitted the ——— as of February 17, 2004 submission.

3. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
[Vol. A1.4, pg. 1778]

4. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 18-748

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE			There is no unexpired patent for this product.		NONE

Exclusivity-Data – NDA 18-748

Code	Reference	Expiration	Labeling Impact
NONE	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	NONE

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: Preserve in collapsible tubes, at controlled room temperature.
- RLD: Store at 15°-30°C (59° - 86°F).
- ANDA: Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]

6. **DISPENSING STATEMENT COMPARISON**

- USP: None
- RLD: None
- ANDA: None

7. **PACKAGE CONFIGURATION**

- RLD: Packaged in 15 gram, 30 gram, and 90 gram tubes.
- ANDA: 15 gram, 30 gram and 90 gram package sizes of Ciclopirox Cream USP, 0.77% are packaged in ——— aluminum closed end tubes with white — caps with piercing tips.

8. **CONTAINER/CLOSURE**

Packaged in Sealed, white, ——————————————— aluminum tubes with white ——————— caps with piercing tips.
[Vol.1.4, page 2031]

9. **FINISHED DOSAGE FORM**

- RLD: A white odorless cream
- ANDA: Smooth, white cream

[Vol. 1.4 pages. 2125 - 2126]

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario, Canada, L6T 1C1 [Vol. 1.4, page 1894]

Date of Review: **Date of Submission: March 12, 2004**

Primary Reviewer: B. Weitzman **Date:** 3/22/04

B Weitzman

Team Leader: **Date:** 3/23/2004

cc: ANDA 76-790
DUP/DIVISION FILE
HFD-613/Bweitzman/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\76790AP.I
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

CHEMISTRY REVIEWS

ANDA 76-790

Ciclopirox Olamine Cream USP, 0.77%

Taro Pharmaceuticals Inc.

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-790

2. REVIEW #: 1

3. REVIEW DATE: 27-OCT-2003, revised 01-DEC-2003

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original application	30-JUN-2003
Acceptable for filing	01-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

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

Address: 5 Skyline Drive, Hawthorne, NY 10532

Representative: Kalpana Rao

Telephone: 914-345-9001

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ciclopirox Olamine Cream, USP

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Loprox® (ciclopirox) Cream 0.77% Medicis
Application Number:	N018748
Strength:	0.77%
Patent Certification:	None
Exclusivity:	None (p.08)

10. PHARMACOL. CATEGORY:
Antifungal

11. DOSAGE FORM:
Cream

12. STRENGTH/POTENCY:
0.77% (as ciclopirox)

13. ROUTE OF ADMINISTRATION:
Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

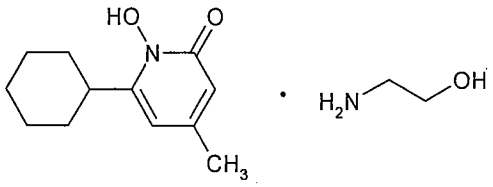
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

2(1*H*)-Pyridinone, 6-cyclohexyl-1-1hydroxy-4-methyl-, compound with 2-aminoethanol (1:1). $C_{12}H_{17}NO_2 \cdot C_2H_7NO$ Mol. Wt. 268.36. CAS No. 41621-49-2.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	23-SEP-2003	By L. Huang
	III			4			USP<661> included.
	III			4			USP<661> included.
	III			4			USP<661> included.
	III			4			USP<661> included. Meets 21 CFR 177.1520
	IV			4			Meets 21 CFR 178

[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-AUG-2003	
Methods Validation	N/A		
Labeling	pending		
Bioequivalence	pending		
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-790

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval (minor amendment).

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)

The reference listed drug for this application is Loprox® Cream (Ciclopirox Olamine Cream), USP 0.77% by Medicis, The Dermatology Company.

The drug substance is Ciclopirox Olamine, USP is a white to off-white powder and conforms to the USP monograph. In addition to USP requirements, Taro included tests for impurities and residual solvents in the drug substance acceptance testing.

The drug product is Ciclopirox Olamine Cream, 0.77% and is for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis; candidiasis; and tinea versicolor.

The drug product contains as excipients; Benzyl Alcohol, NF, Cetyl Alcohol, NF, Cocamide DEA, Lactic Acid, USP, Mineral Oil, USP, Myristyl Alcohol, NF, 2-Octyldodecanol, NF, Polysorbate 60, NF, Purified Water, USP, Sorbitan Monostearate, NF and Stearyl Alcohol, NF.

The drug product is manufactured by

[ ]

The firm explains that homogeneity, viscosity and impurity limits will be established upon the accumulation of additional data. The firm is requested to propose limits based on executed batch.

The bulk drug product is packaged in — 15 g, 30 g and 90 g — sealed, white, ———————————, aluminum tubes with white ——— caps with piercing tips. The firm has requested 24 month expiration date based on the three months accelerated stability and controlled room temperature data. The firm has not provided temperature cycling study results for the drug product and will be requested.

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

C. Basis for Approvability or Not-Approval Recommendation
The deficiencies are related to manufacturing and processing, and the specifications for in-process, finished product and stability.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist, G. Kang/HFD-627/ GK 12/5/03
Chemistry Team Leader, J. Fan/HFD-627/ 12/5/03
Project Manager, A.Vu/HFD-617/

D. CC Block

ANDA #76-790
ANDA #76-790/Division File
Field Copy

Redacted 19 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

10. Microbiological evaluation test specifications are included in the stability testing report on page 2451; however, they are not included in the stability data report. Please explain.

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

1. The bioequivalence and labeling sections of your application are under review and you will be notified separately of any deficiencies.

2. The USP methods for the drug substance and product are the regulatory methods and will prevail in the event of a dispute.

3. A satisfactory compliance evaluation for each of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval.

4. Please provide all available updated drug product long-term room temperature stability data for our evaluation.

Sincerely yours,

12/5/03

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

cc: ANDA 76-790
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/12/2/03 GK 12/5/03

HFD-627/J. Fan, Team Leader/12/2/03 12/5/03

HFD-617/ A. Vu, PM/12/5/03 12/4/03

F/T by :ard/12/5/03

V:\FIRMSNZ\TARO\LTRS&REV\76790NA1.1RD.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-790

Ciclopirox Olamine Cream USP, 0.77%

Taro Pharmaceuticals Inc.

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-790

2. REVIEW #: 2

3. REVIEW DATE: 12-APR-2004

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original application	30-JUN-2003
Acceptable for filing	01-JUL-2003
Deficiency letter based on review #1	09-DEC-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment	17-FEB-2004

7. NAME & ADDRESS OF APPLICANT:

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

Address: 5 Skyline Drive, Hawthorne, NY 10532

Representative: Kalpana Rao

Telephone: 914-345-9001

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ciclopirox Olamine Cream, USP

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Loprox® (ciclopirox) Cream 0.77% Medicis
Application Number:	N018748
Strength:	0.77%
Patent Certification:	None
Exclusivity:	None (p.08)

10. PHARMACOL. CATEGORY:
Antifungal

11. DOSAGE FORM:
Cream

12. STRENGTH/POTENCY:
0.77% (as ciclopirox)

13. ROUTE OF ADMINISTRATION:
Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

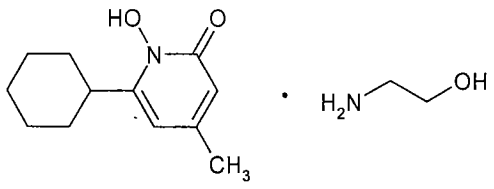
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

2(1*H*)-Pyridinone, 6-cyclohexyl-1-1hydroxy-4-methyl-, compound with 2-aminoethanol (1:1). $C_{12}H_{17}NO_2 \cdot C_2H_7NO$ Mol. Wt. 268.36. CAS No. 41621-49-2.

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	23-SEP-2003	By L. Huang
	III			4			USP<661> included.
	III			4			USP<661> included.
	III			4			USP<661> included.
	III			4			USP<661> included. Meets 21 CFR 177.1520
	IV			4			Meets 21 CFR 178

[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-AUG-2003	
Methods Validation	N/A		
Labeling	Acceptable	23-MAR-2004	B. Weitzman
Bioequivalence	Pending		
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Minor Amendment

The Chemistry Review for ANDA 76-790

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval (minor amendment).

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)

The reference listed drug for this application is Loprox® Cream (Ciclopirox Olamine Cream), USP 0.77% by Medicis, The Dermatology Company.

The drug substance is Ciclopirox Olamine, USP is a white to off-white powder and conforms to the USP monograph. In addition to USP requirements, Taro included tests for impurities and residual solvents in the drug substance acceptance testing.

The drug product is Ciclopirox Olamine Cream, 0.77% and is for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis; candidiasis; and tinea versicolor.

The drug product contains as excipients; Benzyl Alcohol, NF, Cetyl Alcohol, NF, Cocamide DEA, Lactic Acid, USP, Mineral Oil, USP, Myristyl Alcohol, NF, 2-Octyldodecanol, NF, Polysorbate 60, NF, Purified Water, USP, Sorbitan Monostearate, NF and Stearyl Alcohol, NF.

The drug product is manufactured by [redacted]

[redacted] This issue needs to be resolved.

Originally, the bulk drug product is packaged in [redacted] 15 g, 30 g and 90 g [redacted] sealed, white, [redacted] aluminum tubes with white [redacted] caps with piercing tips; however, [redacted] and is withdrawn with 17-FEB-2004 amendment.
The firm has requested 24 month expiration date based on the three months accelerated stability and 12 months controlled room temperature data. The firm has provided satisfactory temperature cycling study results for the drug product.

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

C. Basis for Approvability or Not-Approval Recommendation
The deficiencies are related to manufacturing and processing, and the specifications for in-process and stability.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist, G. Kang/HFD-627/GK 5/6/04
Chemistry Team Leader, J. Fan/HFD-627/
Project Manager, A.Vu/HFD-617/

D. CC Block

ANDA #76-790
ANDA #76-790/Division File
Field Copy

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

First three production batches and one batch yearly thereafter will be placed on stability. The expiration date will be extended based on satisfactory full long-term stability data obtained from at least three production batches. The firm will withdraw from commerce any batch which falls outside of the specifications (pp.3264).

E. Expiration Dating Period

Taro proposed 24-month expiration dating based on 3 months accelerated and controlled room temperature data.

30. MICROBIOLOGY

Review Status: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Review Status: N/A

Both the drug substance and product are listed in the USP. FDA method validation is not required.

32. LABELING

Review Status: Acceptable on 23-MAR-2004

Labeling section was reviewed by B. Weitzman and found acceptable.

33. ESTABLISHMENT INSPECTION

Review Status: acceptable on 18-AUG-2003

34. BIOEQUIVALENCE

Review Status: pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review Status: satisfactory

A wavier was submitted on page 2487.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-790 APPLICANT: Taro Pharmaceuticals Inc.

DRUG PRODUCT: Ciclopirox Olamine Cream USP, 0.77% (as ciclopirox)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]
2.
3.

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

1. The bioequivalence section of your application is under review and you will be notified separately of any deficiencies.

2. Please provide all available updated drug product long-term room temperature stability data for our evaluation.

Sincerely yours,

5/6/04

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

cc: ANDA 76-790
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/ GR 5/6/04

HFD-627/J. Fan, Team Leader/ 5/6/04

HFD-617/ A. Vu, PM/

F/T by :

V:\FIRMSNZ\TARO\LTRS&REV\76790NA1.2RD.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-790

Ciclopirox Olamine Cream USP, 0.77%

Taro Pharmaceuticals Inc.

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-790

2. REVIEW #: 3

3. REVIEW DATE: 8-SEP-2004, Revised 06-APR-2005

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original application	30-JUN-2003
Acceptable for filing	01-JUL-2003
Deficiency letter based on review #1	09-DEC-2003
Minor amendment	17-FEB-2004
Deficiency letter based on review #2	07-MAY-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment	02-JUN-2004

7. NAME & ADDRESS OF APPLICANT:

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

Address: 5 Skyline Drive, Hawthorne, NY 10532

Representative: Kalpana Rao

Telephone: 914-345-9001

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ciclopirox Olamine Cream, USP

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Loprox® (ciclopirox) Cream 0.77% Medicis
Application Number:	N018748
Strength:	0.77%
Patent Certification:	None
Exclusivity:	None (p.08)

10. PHARMACOL. CATEGORY:
Antifungal

11. DOSAGE FORM:
Cream

12. STRENGTH/POTENCY:
0.77% (as ciclopirox)

13. ROUTE OF ADMINISTRATION:
Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

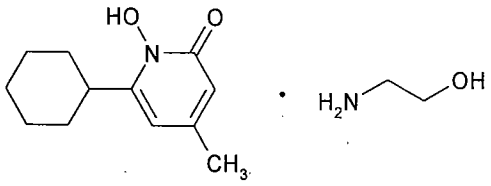
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

2(1*H*)-Pyridinone, 6-cyclohexyl-1-1hydroxy-4-methyl-, compound with 2-aminoethanol (1:1). $C_{12}H_{17}NO_2 \cdot C_2H_7NO$ Mol. Wt. 268.36. CAS No. 41621-49-2.

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	26-OCT-2004	By L. Huang
	III			4			USP<661> included.
	III			4			USP<661> included.
	III			4			USP<661> included.
	III			4			USP<661> included. Meets 21 CFR 177.1520
	IV			4			Meets 21 CFR 178

[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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2/3/04	
Methods Validation	N/A		
Labeling	Acceptable	23-MAR-2004	B. Weitzman
Bioequivalence	Acceptable	29-MAR-2005	C. Kim
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Minor Amendment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-790

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is 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)

The reference listed drug for this application is Loprox® Cream (Ciclopirox Olamine Cream), USP 0.77% by Medicis, The Dermatology Company.

The drug substance is Ciclopirox Olamine, USP is a white to off-white powder and conforms to the USP monograph. In addition to USP requirements, Taro included tests for impurities and residual solvents in the drug substance acceptance testing.

The drug product is Ciclopirox Olamine Cream, 0.77% and is for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis; candidiasis; and tinea versicolor. The drug product contains as excipients; Benzyl Alcohol, NF, Cetyl Alcohol, NF, Cocamide DEA, Lactic Acid, USP, Mineral Oil, USP, Myristyl Alcohol, NF, 2-Octyldodecanol, NF, Polysorbate 60, NF, Purified Water, USP, Sorbitan Monostearate, NF and Stearyl Alcohol, NF.

The drug product is manufactured by

Originally, the bulk drug product is packaged in — 15 g, 30 g and 90 g — sealed, white, — aluminum tubes with white — caps with piercing tips; however, — and was withdrawn with 17-FEB-2004 amendment.

The firm has requested 24 month expiration date based on the three months accelerated stability and 12 months controlled room temperature data. The firm has provided satisfactory temperature cycling study results for the drug product.

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

Ciclopirox Olamine Cream USP, 0.77% is supplied in 15 g, 30 g and 90 g tubes. According to dosage and administration information described in packaging insert, this drug product is applied by massaging into the affected skin twice daily and the maximum treatment of therapy is 4 weeks.

Therefore, the maximum daily dose (MDD) of Ciclopirox Olamine Cream USP, 0.77% is calculated as follows:

90 g (the largest size)/28 days (4 weeks) = 3.21 (g)
3.21 g x 0.77% (active in the drug product) = 24.7 (mg)
24.7 mg x 1.3% (average absorption in pharmacokinetic studies in human) = **0.32 mg (MDD)**

-The drug substance: based on the ICH Guideline Q3A dated February 2003
IT is 0.10% for any single unknown impurities (unspecified).
QT is 0.15% for any specified identified or specified unidentified impurity.

-The drug product: based on the ICH Guideline Q3B (R) dated November 2003
IT is 1.0% for any single unknown impurities (unspecified).
QT is 1.0% for any specified identified or specified unidentified impurity.

C. Basis for Approvability or Not-Approval Recommendation
The application is approvable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block G/C 4/8/05
Chemist, G. Kang/HFD-627/4/6/05
Chemistry Team Leader, J. Fan/HFD-627/4/7/05 4/8/05
Project Manager, A.Vu/HFD-617/CKiester for/4/7/05

D. CC Block
ANDA #76-790
ANDA #76-790/Division File
Field Copy

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

32. LABELING

Review Status: Acceptable on 23-MAR-2004

Labeling section was reviewed by B. Weitzman and found acceptable.

33. ESTABLISHMENT INSPECTION

Review Status: acceptable on 2/3/04

34. BIOEQUIVALENCE

Review Status: acceptable on 29-MAR-2005

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review Status: satisfactory

A wavier was submitted on page 2487.

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-790
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/4/6/05 GK 4/8/05

HFD-627/J. Fan, Team Leader/4/7/05 4/9/05

HFD-617/ A. Vu, PM/CKiester for/4/7/05

F/T by :ard/4/7/05 4/11/05

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TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

BIOEQUIVALENCE REVIEW

Clinical Review Section

Review of

A Bioequivalence Study

with

Clinical Endpoints

ANDA # 76-790
Taro Pharmaceuticals USA

Ciclopirox Olamine Cream, USP, 0.77% (as ciclopirox)

Carol Kim, Pharm.D.
Clinical Review Team

Submission dates reviewed: 6/30/03
10/21/04 (dataset)

Date of Review: 3/28/05
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CLINICAL REVIEW

Clinical Review Section

Table of Contents

Clinical Review for ANDA 76-790

Executive Summary

This double-blind, randomized, single-center, parallel-group study demonstrates that Taro's Ciclopirox Olamine Cream 0.77% is safe and bioequivalent to Loprox® 0.77 Cream, in the treatment of tinea pedis. The FDA statistical review confirms that the 90% Confidence Interval (CI) of the proportional difference in therapeutic cure rates between the test and reference products at the 2 weeks follow-up visit (Visit 3, Week 6) is (-0.054,+.141), which is within the bioequivalence limits of -0.20 and 0.20. A total of 462 patients with mycologically confirmed tinea pedis were randomized and treated with the study drugs. Based on the FDA statistical review, all 462 patients were included in the Modified Intent-to-Treat (MITT)[1] population, and 406 were included in the Evaluable Population (EP)[2].

I. Recommendation on Approval

The data submitted to ANDA 76-790, using the primary endpoint of therapeutic cure rate at Week 6 (Visit 3, 2 weeks post treatment visit), are adequate to demonstrate bioequivalence of Taro's Ciclopirox Olamine Cream, 0.77%, with the reference listed drug, Medicis' Loprox® 0.77% Cream. Therefore, the test product is recommended for approval.

II. Summary of Clinical Findings

The data presented in this ANDA 76-790 demonstrate that Taro Pharmaceuticals USA, Inc.'s Ciclopirox Olamine Cream, 0.77%, is bioequivalent to the reference listed drug, Loprox® (Ciclopirox) Cream, 0.77%.

A. Brief Overview of Clinical Program

The study #CPO 0208 was a randomized double blind comparative study of Taro's Ciclopirox Olamine Cream, 0.77%, versus the reference listed drug, Loprox® (Ciclopirox) Cream, 0.77%, in the treatment of tinea pedis. Four hundred sixty two (462) patients with tinea pedis confirmed by fungal culture were randomized to receive the test, reference, or placebo/vehicle cream twice daily for 28 days (4 weeks).

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[1] Included all randomized patients who met inclusion/exclusion criteria, diagnosed with tinea pedis, received at least one dose of study medication, and returned for at least one post-baseline visit evaluation.

[2] Included all randomized patients who met inclusion/exclusion criteria, diagnosed 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.

B. Comparative Efficacy

The primary endpoint of this product is a therapeutic cure at 2 weeks follow-up visit (Visit 3, Week 6) after completion of 4 weeks 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 total clinical score (sum of severity scores on signs and symptoms) at visit 3 is 2 or less with a score of no more than 1 for any of the 6 clinical parameters. 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 end of treatment visit (visit 2) and at the post-treatment visit (visit 3).

Reviewer's Comment: *Mycological cure should be defined as both negative KOH and fungal culture at visit 3 (week 6) only.*

According to the FDA statistical analysis, therapeutic cure rates in the Evaluable Population (EP) at Visit 3 were 50% in the test group and 46% in the reference group. The 90% CI for proportional difference in therapeutic cure rates between the two active products was within the bioequivalence limits of -0.20 and +0.20. The FDA statistical analysis for the EP included the outcome of mycological results from Visit 3 only.

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 97 adverse events occurred in the study (37 in the test, 36 in the reference and 24 in the vehicle group). The most common adverse event reported in the study was skin related application site reaction (6.3% Test, 4.5% Ref, and 9.8% Vehicle). These patients experienced mostly burning and itching at the application site and they were similar in both test and reference groups.

Two patients (T: #226, Ref: #890) discontinued the study treatment after receiving at least one day of study treatment due to increased burning and inflammation at the application site.

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 recurrences[3]. The demonstration of hyphae on direct microscopy and isolation of dermatophyte on fungal culture confirm the diagnosis.

A. Drug Established Name, Drug Class,

Drug Established Name: Ciclopirox Olamine Cream, 0.77%
Drug Class: Antifungal agent

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

Reference Drug (NDA number): Loprox® Cream (NDA 18748), Medicis
Date of approval: 12/30/82
Approved indication(s): Topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum, T. mentagrophytes, Epidermophyton floccosum and Microsporum canis;* in the treatment of cutaneous candidiasis (moniliasis) caused by *Candida albicans; and tinea (pityriasis) versicolor caused by Malasseszia furfur.*

Recommended dosing regimens: Gently massage into the affected areas twice daily. If a patient shows no clinical improvement after 4 weeks of treatment, the diagnosis should be re-determined.

C. Regulatory Background

The following submissions have been reviewed by the OGD for Ciclopirox:

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

none

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

Submission	Submission date	Name of the Product/Sponsor
CD# 02-472	August 14, 2002	Ciclopirox Gel, 0.77% ———
IND ———	June 6, 2000	Ciclopirox Olamine Cream, 1% ———
IND ———	October 31, 2000	Ciclopirox Olamine Lotion, 1% ———
CD# 01-016	January 5, 2001	Ciclopirox Nail Varnish ———
P02-058	November 13, 2002	Ciclopirox Topical Gel, 0.77%———
CD#01-128	March 1, 2001	Ciclopirox Topical Solution, 8%———

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

3. Previous ANDA submissions for same or related product

Submission	Submission date (approval date)	Name of the Product/Sponsor
ANDA 76-422	8/5/02 (8/6/04)	Ciclopirox Suspension, 0.77%; Altana
ANDA 76-435	6/18/02 (12/29/04)	Ciclopirox Cream, 0.77%; Altana
ANDA 77-092	3/17/04 (pending review)	Ciclopirox Suspension, Taro

D. Other Relevant Information

The innovator's product was reformulated (8/17/01) by deleting inactive ingredient cocomide DEA and substituting light mineral oil for mineral oil.

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	[redacted] M.D.	[redacted]	462

Study Period: March 17, 2003 to May 15, 2003

Enrollment: Of 826 patients with clinical evidence of tinea pedis, four hundred sixty-two (462) patients were eligible for randomization into the study.

A total of 986 patients were initially screened and 160 patients failed to meet the screening criteria. Three hundred sixty four (364) patients failed to meet the randomization criteria due to negative baseline culture (363 patients) and contamination of baseline culture specimen (1 patient).

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: ANDA 76-790, Vol. 1.1-1.3, submitted on 6/30/03

Study Amendments: The OGD asked the sponsor to provide additional data on October 15, 2004. In response, the sponsor submitted the requested information in the study amendment dated October 21, 2004.

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 inspection history on the same clinical site (ANDAs ———————).

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

Dr. ——— declared that he is in good standing of a professional medical or dental association as defined in Division 5 of the Food and Drug Regulations and signed the statement that he was to conduct the study in accordance with Good Clinical Practices.

The sponsor's original, amended protocols, and consent forms were reviewed and approved by the Ethics Review Committee prior to initiation of the study.

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

D. Evaluation of Financial Disclosure: Dr. ——— submitted signed financial disclosure documents certifying that he has not entered into any financial arrangement with the sponsor and declared that he has not received significant payment of other sorts as defined in 21 CFR 54.2 (f).

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The sponsor's study confirms 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 #CPO 0208) 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 week 6 follow-up visit (2 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

This protocol has not been previously reviewed by the OGD prior to submission.

Protocol Review (CPO 0208):

- The sponsor's protocol was amended two times prior to this submission. The original protocol (# CPO 0208) dated October 29, 2002 was approved

by the Ethics Review Committee on 12/2/02. The sponsor revised their protocol (Amendment #1) on December 11, 2002 by incorporating "on feet" next to the word "topical" in the exclusion criteria.

- Protocol Amendment #2 was issued on 2/3/03. This amendment made minor administrative changes into the protocol.

Sponsor's protocol#: CPO 0208

Title: A 3-Way, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Therapeutic Equivalence of Ciclopirox Olamine Cream, 0.77% Manufactured by Taro Pharmaceuticals Inc. and Loprox® Cream) Manufactured by Medicis in the Treatment of Clinically Diagnosed and Mycologically Confirmed Tinea Pedis

Objectives: The primary purpose of this study was to demonstrate that Taro's ciclopirox olamine cream, 0.77% was bioequivalent to Medicis' Loprox® cream (RLD) and to show that both were superior to placebo in the treatment of clinically symptomatic and mycologically confirmed tinea pedis. The secondary objective of the study was to compare the adverse event profile of the two creams to establish that the products had no unanticipated adverse effects.

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

1. Test: Ciclopirox Olamine Cream, 0.77%, Taro Pharmaceuticals Inc., administered topically twice daily for 28 days; lot #S115-53807
2. Reference: Loprox® Cream (ciclopirox), 0.77%, Medicis, administered topically twice daily for 28 days; lot #40A291
3. Vehicle/Placebo: Taro's vehicle, administered topically twice daily for 28 days; lot #S115-53891

Blinding:
The study drug supplies were packaged in identical boxes (patient kits) identified by a patient number. The patient kits were labeled and packaged in identical boxes so that neither the patient nor the investigator could identify the treatment.

Each kit contained the standard label with the following information: protocol number, patient number, reference to directions for use, a note that drug is for investigational use only, and storage condition. Packaging and labeling of the study drugs were performed by the sponsor. The randomization code was kept at Taro Pharmaceuticals.

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 or non-pregnant, non-nursing female patients
3. Clinical evidence of tinea pedis with at least mild scaling (severity score of 2).
4. Women of childbearing potential must have a negative urine pregnancy test result upon entry into the study and agree to use a medically accepted form of birth control.
5. Subsequently, culture positive for *T rubrum, T, mentagrophytes,* or *Epidermophyton floccosum* must be demonstrated for the patient to be considered evaluable.
6. Patients must be willing and able to comply with all requirements of the protocol.
7. Signed informed consent.

Exclusion Criteria

1. Pregnancy or lactation
2. Patient's decision to leave the study for any reason
3. Bacterial or viral skin infections on feet other than tinea pedis
4. Insulin dependent diabetes mellitus
5. Known allergy or sensitivity to ciclopirox olamine, related compounds, or to any component of the formulation
6. Severe thick (hyperkeratotic) scaly lesions
7. Current use, or use within 30 days prior to enrollment, of oral antibiotics or oral or topical antifungal (on feet) preparations
8. Use of any topical (on feet) or systemic corticosteroids within 30 days prior to enrollment.
9. Any other dermatological condition which might impair diagnosis.
10. Development of an intercurrent condition or complication which would affect the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the investigator.
11. Failure to comply with the protocol
12. Negative baseline culture or other violation of inclusion/exclusion criteria

Criteria for continuation of study:

The definitive determination of all fungal cultures was made after approximately 4 weeks of incubation. Patients with negative pre-treatment fungal cultures were excluded from the analyses but followed for the evaluation of adverse events. All enrolled patients were to be seen at 4 weeks after initiation of the study treatment. Only those patients with positive baseline fungal cultures continued for the 6-week visit and were included in the bioequivalence analyses.

Patients were not permitted to take any oral antibiotics or antifungal agents, or apply any other topical medications to the affected areas for 6 weeks of the study.

If any of the above medications were used during the study, the patient was designated as a protocol violation.

Compliance

Compliance with the protocol requirements was assessed by the principal investigator at each visit by questioning the patient about study drug use, and other medication use. This information was captured on the case report form.

Compliance with study drug regimen was further assessed by evaluating the drug application section of the patient's diary. Patients not complying with the protocol were excluded from the analysis.

Procedures/Observations, and safety measures:

Visit 1(Day 1); Screening and Treatment day

The medical history and foot assessments were completed. Patients underwent laboratory testing, and a urine pregnancy test for female patients with childbearing potential. 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

STAT 10% potassium hydroxide (KOH) smear was examined microscopically for the evidence of fungus. Mycological cultures were examined for *Tinea rubrum, Tinea mentagrophytes,* or *E. floccosum.* Other organisms may be identified but the culture results would be 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 5-point scale. Patients recorded the severity of symptoms of itching and burning and the investigator evaluated the severity of erythema, scaling (desquamation), fissuring, and bullae formation using the same 5-point scale as follows:

Investigator's evaluation	Patient's evaluation	Scale
• erythema	Itching	0=none
• scaling (desquamation)	Burning	1=mild
• fissuring		2=moderate
• bullae		3=moderately severe
		4=severe or extensive

Visit 2 (Day 28); End of treatment (Week 4) visit and Visit 3 (Day 42); follow-up Week 6 visit, Primary Endpoint Visit

Four weeks (Day 28 ±4 days) and 6 weeks (Day 42 ±3 days) after initiation of the study treatment, patients returned for repeat clinical and mycological assessments on the study foot at each visit. 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. At the end of treatment (Week 4) visit, women of childbearing potential repeated a pregnancy test.

At the end of treatment (Week 4) visit, patients were instructed to return the used or unused study medication. Patients were questioned concerning possible adverse drug effects and compliance with the protocol at each visit. Any adverse events or changes to concomitant medications were documented.

Upon conclusion of the study the investigator was instructed to return all unused and used medication kits to Taro.

Endpoints:

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

Definitions:

- Clinical Cure: a total clinical score (sum of severity scores on signs and symptoms) at visit 3 is 2 or less with a score of no more than 1 for any of the 6 clinical parameters.

- Mycological Cure: a negative KOH wet mount for pseudohyphae and a negative culture for tinea pedis species at the end of treatment visit (visit 2) and the post-treatment visit (visit 3). If a patient had a positive KOH wet mount and/or a positive culture for tinea pedis at either visit 2 or visit 3, he/she was recorded as a mycological failure.

Reviewer's Comments: *The sponsor combined mycological results from both visits 2 and 3 for evaluation of a mycological cure. For the primary endpoint evaluation, mycological results from only visit 3 (Week 6) should be analyzed.*

- Therapeutic cure: Both a clinical and mycological cure.

Patients who were discontinued early from the study because of an inadequate clinical or mycological response and patients who discontinued study drug due to a treatment-related adverse event were counted as clinical, mycological, and therapeutic failures.

The secondary efficacy parameters were evaluated by the sponsor as follows:
• proportion of patients with a clinical or mycological cure at Visits 2 and 3 combined.

Statistical analysis plan

Primary Endpoint: All patients who were considered evaluable were included in the primary endpoint analysis. The primary endpoint is the therapeutic cure. Secondary endpoint evaluation was performed on clinical and mycological cure rates.

Sample Size: At least 375 patients were proposed to allow 150 patients per active treatment group and 75 patients in the vehicle/placebo group complete the study.

Analysis: For the bioequivalence analysis, confidence interval was constructed for the difference in the proportions of therapeutic cure rates between the test and reference products at Visit 3 (Day 42). The confidence interval was calculated using Blackwelder's method with Yates' continuity correction. Bioequivalence was established if this 90% confidence interval was contained within the interval of –20% to +20%. The analysis in the PP population was considered primary and that in the ITT population as supportive.

All statistical procedures were performed by two-tailed tests using the SAS (version 8). 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 as follows:

Intent-to-treat (ITT): clinically symptomatic patients randomized to treatment, had positive baseline fungal cultures, applied at least one dose of study drug, and met all other enrollment criteria.

In this analysis, patients without data for visits 2 and 3 were considered mycological, clinical, and therapeutic failures and patients without data for visit 3 had their visit 2 results carried forward.

Reviewer's Comments: *The sponsor's protocol proposed to include patients with at least one post baseline return visit in the ITT population. However, patients with no post baseline data (missing visits 2 and 3) were carried forward as therapeutic failures in the ITT population analysis. These patients should instead*

be excluded from both ITT and PP populations.

Per-protocol (PP)
Eligible patients with a positive baseline culture, have clinical and mycological data for both Visits 2 and 3 within specified visit window, and have not violated protocol.

Reviewer's Comments: *Patients who missed visit 2 should not be excluded from the PP analysis if data are available for visit 3. A patient should be considered a clinical, mycological, and therapeutic cure based on Visit 3 data only for determination of bioequivalence.*

Any patient that did not return for the follow-up visits because of early declared treatment failure or study drug related adverse event was included as a clinical, mycological, and therapeutic failure. Female patients with pregnancy test positive during the 4 week period of study treatment were excluded from the efficacy and therapeutic equivalence analyses.

Reviewer's Comments: *Patients that discontinued because of study drug related adverse events should be excluded from the PP analysis and included in the ITT analysis using LOCF.*

Discussion of compliance:

The sponsor did not clearly define treatment compliance for this study.

Reviewer's Comments: *Although this reviewer specifically asked for the definition of treatment compliance that was used for this study on October 15, 2004, the sponsor only provided a dataset with each patient line listing of "yes" or "no" for the treatment compliance. Upon the review of this dataset, this reviewer noted that the sponsor considered those patients that missed up to 9 doses (87% compliant rate) as treatment compliant. Patients that missed 17 doses (70% compliant rate) or more were not considered as treatment compliant by the sponsor. No patient missed between 10 and 16 doses in this study. Based on this observation, this reviewer agrees with the sponsor's decision to consider those patients that missed 17 doses or more as non-treatment compliant and exclude from the PP population.*

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.*

Demographics

Of the 462 treated patients, 306 (66%) were Caucasian, 51 (11%) were Black, 94 (20%) were Hispanic, and 11 (2%) were classified as "other". Baseline demographics, age, and race in the ITT population were similar in all treatment groups. The mean age was 40 (19-82), 39.6 (19-79) and 39.5 (18-81) 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 462 randomized patients (per sponsor)

Characteristic		TARO (N=186)	RLD (N=187)	Vehicle (N=89)	Total (N=462)
Race	Caucasian	123 (66%)	125 (67%)	58 (65%)	306 (66%)
	Black	19 (10%)	22 (12%)	10 (11%)	51 (11%)
	Hispanic	39 (21%)	36 (19%)	19 (21%)	94 (20%)
	Other	5 (3%)	4 (2%)	2 (2%)	11 (2%)
Age (years)	Mean (Std)	40 (12.0)	39.6 (12.9)	39.5 (13.4)	39.7 (12.6)
	Min - Max	19 - 82	19 - 79	18-81	18-82
Gender	Male	148 (80%)	143 (76%)	70 (79%)	361 (78%)
	Female	38 (20%)	44 (24%)	19 (21%)	101 (22%)

Baseline disease severity

The Sponsor tabulated mean severity scores for each signs and symptoms 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	Scaling		Erythema		Fissuring		Bullae		Itching		Burning		Total*	
		mean	SE	mean	SE	mean	SE	mean	SE	mean	SE	mean	SE	mean	SE
TARO	186	2.24	0.04	1.52	0.04	0.69	0.04	0.03	0.02	2.28	0.07	0.07	0.03	6.82	0.13
RLD	187	2.30	0.04	1.50	0.04	0.69	0.04	0.01	0.01	2.35	0.07	0.14	0.04	7.01	0.13
VEHICLE	89	2.25	0.06	1.51	0.05	0.70	0.06	0.04	0.03	2.18	0.10	0.09	0.04	6.76	0.19
For difference between treatment groups p=		0.51		0.97		0.99		0.44		0.36		0.26		0.48	
* Sum of individual sign/symptom scores for each subject															

Reviewer's Comment: *There was no statistically significant difference between treatment groups for individual mean baseline clinical signs and symptoms scores or total signs and symptoms scores at baseline in the ITT population.*

Baseline Fungal Culture

The majority of patients had the baseline fungal culture positive for *Trichophyton rubrum* (84%) in the sponsor's ITT population. The other dermatophytes isolated were *T. Mentagrophytes* (11.5%) and *Epidermophyton Floccosum* (4.5%). 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=0.62).

Results

According to the study amendment dated 10/21/04, nine hundred eighty six (986) patients were initially screened. One hundred sixty (160) patients were considered as screening failures (violation of inclusion/exclusion criteria) at baseline. Of 826 patients eligible for enrollment, a total of 462 patients were included in the ITT population; 186 in the test, 187 in the reference, and 89 in the vehicle groups, respectively. Three hundred sixty four (364) patients were excluded from the ITT population due to negative baseline culture or contaminated culture specimen.

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
Intention to Treat Population				
All randomized patients	**186**	**187**	**89**	**462**
Missing visits 2 and 3	16	20	6	42
Other protocol violations[1]	4	8	1	13
Per Protocol Population				
Visit 2: 24-32 days; visit 3: 39-45 days	**166**	**159**	**82**	**407**

[1] used antibiotics prior to visit 2, no Visit 3 or missed Visit 3, missed more than 2 weeks of study drug application, Visit 3 out of 39-45 day window

Table IV: Primary Efficacy Analysis: Therapeutic Cure[1] Rate at Visits 2 and 3 combined (per sponsor)

Parameter	TARO	RLD	90% C.I. for Bioequivalence of Taro's product to Loprox®		
Per-Protocol Patients					
Visit 2 and 3 combined	(N=166)	(N=159)			
Therapeutic Cure	**60 (36%)**	**59 (37%)**	**(-10.4%, 8.4%)**		
Clinical Cure	105 (63%)	100 (63%)	(-9.1%, 9.8%)		
Mycological Cure	95 (57%)	90 (57%)	(-9.0%, 10.3%)		
Intent-to-Treat Patients					
	TARO	RLD	Vehicle	P-Value (2-sided cc Z-test)	
Visit 2 and 3 combined	(N=186)	(N=187)	(N=89)	T vs. Vehicle	Ref vs. Vehicle
Therapeutic Cure	60 (32%)	60 (32%)	9 (10%)	<0.001	<0.001
Clinical Cure	106 (57%)	103 (55%)	37 (42%)	0.02	0.05
Mycological Cure	96 (52%)	94 (50%)	18 (20%)	<0.001	<0.001

[1] Mycological cure defined as culture and KOH negative at visit 2 and visit 3. Clinical cure defined as combined sign/symptom score no more than 2 and no more than 1 on any clinical parameter at visit 3. Therapeutic cure defined as having both a clinical and mycological cure.

Two patients with adverse events missing both visit 2 and visit 3 were retained in this analysis and designated as mycologic, clinical, ad therapeutic failures. .

Reviewer's Comments:

- *The sponsor included two patients in the PP population as treatment failures. Patient #890 (Ref) experienced severe inflammation of foot after application of study cream for 5 days. Patient #226 (test) experienced moderate burning and the application site was swollen after receiving one day of the study cream. They were instructed by the investigator to stop the study medication and discontinue from the study.*

  Since patient #890 discontinued the study due to lack of treatment response after reasonable use of the study medication, this reveiwer agrees with the sponsor's decision to include this patient in the PP population analysis as a treatment failure.

  However, patient #226 had to discontinue the study treatment due to serious application site reaction after receiving only 2 doses of the study medication. Since this adverse event was considered as an allergic reaction to the study treatment, this reviewer disagrees with the sponsor's decision to retain this patient in the PP population as a treatment failure. This patient should be excluded from the PP population.

- *The sponsor included those patients that missed visits 2 and 3 in the ITT population analysis using the Last-Observation-Carried-Forward (LOCF). Since they have no post-baseline visit data, they should be excluded from the ITT population but included in the safety population. The sponsor appropriately excluded them from the PP population.*

- *The sponsor's definition of the ITT population requires that baseline cultures be positive, similar to the usual FDA definition of a modified intent-to-treat (MITT) population. However, only patients who have received at least one dose of the study treatment and completed foot assessment for at least one post-baseline return visit should be included.*

- *For assessment of bioequivalence, therapeutic cure should be evaluated at week 6. A patient is considered a mycological cure if both KOH and fungal culture results are negative at visit 3 (week 6) only. The sponsor's evaluated clinical cure is acceptable. A patient is considered a therapeutic cure if she or he is designated as both clinical and mycological cure at visit 3 (week 6) only.*

- *The cure rates of the reference cream reported in this study appear to be much lower than the cure rates reported in clinical studies used for the approval of the innovator's product (NDA 18-748).*[4] *Although most of the patients in Taro's study had the interdigital form of the disease (63%), approximately 36% of the patients had the plantar type of tinea pedis. Since it is more difficult to treat plantar type of tinea pedis with a 1 month course of topical therapy, many of the study patients with plantar type tinea pedis would not likely have resulted in cure by week 6 visit.*

D. Bioequivalence Conclusion

Based on the FDA statistical analyses, the study demonstrates that the 90% CI for the proportional difference in therapeutic cure rates between the test and the reference products at visit 3 (Week 6) is (-0.054, 0.141), which is within the bioequivalence limits of (-.20, +.20). A patient was considered a clinical cure by the sponsor if a total clinical score (sum of severity scores on signs and symptoms) at visit 3 is 2 or less with a score of no more than 1 for any of the 6 clinical parameters. A patient was considered a mycological cure if he or she had negative KOH and negative fungal culture for tinea pedis species at both visits 2 and 3.

Reviewer's Comments:

- *The recommended primary endpoint for this product is a therapeutic cure at Visit 3 (week 6) only although the OGD has previously accepted an endpoint of therapeutic cure at both end of treatment and at 2 weeks follow-up (e.g. both week 4 and week 6).*
- *An FDA statistical consult was requested for reanalysis and verification of the sponsor's data, using week 6 data.*

[4] In placebo-controlled study (protocol #302) for treatment of tinea pedis, therapeutic cure (both clinical and mycological cure) rates ranged 20% to 73%. In active controlled study (protocol #306) with Lotrimin®, therapeutic cure rates ranged 44% to 92%.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed no significant difference between the generic and reference products with regard to the adverse events reported.

B. Description of Adverse Events

The overall incidence of adverse events by severity was similar in both active treatment groups. A total of 97 adverse events occurred in the study (37 in the test, 36 in the reference, and 24 in the vehicle group). Skin related application site reactions (6.3% test, 4.5% reference, and 9.8% vehicle) were the most frequent adverse events reported in the study. Burning and itching at the application site were the most frequent skin-related adverse events both in the test and reference groups.

No death occurred in the study. Four patients (2 in the test and 2 in the reference group) experienced adverse events that were considered serious by the investigator. Of those four patients, one patient (887; test) experienced severe asthmatic congestion due to fire in the home, and one patient (714; test) had pace maker insertion. One patient (647; reference) had dental abscess and was treated with antibiotics. One patient (389; reference) had to discontinue the study treatment due to severe itching after receiving two weeks of study drug. No patient experienced serious adverse event in the vehicle group.

Except for patient #389 (reference), none of above adverse events were considered study treatment related.

The sponsor's summary of frequency of adverse events is listed below.

Adverse Events Summary by Event in Enrolled Patients (per sponsor)

	Events	Pts				*Severity (All AEs)					
Test	37	332				1	2	3	Total		
Ref	36	331			Test	23	12	2	37		
Veh	24	163			Ref	29	5	2	36		
Total	97	826			Veh	21	3	0	24		
					Total	73	20	4	97		
				**MEDRA Classification							
	1	2	3	4	5	6	7	8	9	Total	
Test	1	1	1	0	4	3	5	21	1	37	
Ref	0	3	0	2	3	3	9	15	1	36	
Veh	0	0	0	0	1	1	5	16	1	24	
Total	1	4	1	2	8	7	19	52	3	97	

	Relation to Treatment						*Severity (Skin Related AEs only)				
	No	Yes	Total				1	2	3	Total	
Test	18	19	37			Test	15	6	0	21	
Ref	22	14	36			Ref	10	4	1	15	
Veh	8	16	24			Veh	14	2	0	16	
Total	43	49	97			Total	39	12	1	52	
					^Relation to Skin						
	0	1	2	3	4	5	6	7	8	9	Total
Test	16	5	6	1	0	2	1	4	0	2	37
Ref	21	4	4	2	1	0	0	3	1	0	36
Veh	8	6	8	0	2	0	0	0	0	0	24
Total	45	15	18	3	3	2	1	7	1	2	97

*Severity: 1=mild 2=moderate 3=severe

**MEDRA Classification: 1=Cardiac disorders 2=Gastrointestinal disorders 3=Injury, poisoning and procedural complications 4=Metabolism and nutrition disorders 5=Musculoskeletal and connective tissue disorders 6=Nervous system disorders 7=Respiratory, thoracic and mediastinal disorders 8=Skin and subcutaneous tissue disorders 9=Surgical and medical procedures

^Relation to Skin: 1=Burning 2=Itching 3=Irritation 4=Stinging 5=Swollen 6=Pain 7=Inflammation 8=Desquamation 9=Other 0=Unrelated

Reviewer's Comment: *The reported frequency of skin related adverse events in this study is comparable between the test and reference groups.*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report

Dr. ——— office was previously inspected by the DSI for ANDA ——— ———. Based on the final report issued on ——— ———, a Form FDA-483 was issued because the investigator did not comply with the requirement for retention of study drugs as per 21 CFR 320.38 and 320.63 at this site. Other than retention sample issue, the study was acceptable for the review.

A subsequent inspection——— for ——— did not find any deficiency related to retention samples, and no Form FDA-483 was issued although the sponsor had not provided a sealed copy of the randomization code to the site.

Reviewer's Comment: *The sponsor has previously been advised to comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63 and to maintain a sealed code for use by the FDA in future studies. The brief description of the sponsor's plan for retention samples appears acceptable.*

B. Review of the FDA Statistical Report (3/23/05)

The conclusion of the FDA statistical analysis confirms the bioequivalence of the test and the reference products. The 90% CI of the therapeutic cure rates for the evaluable population at the 2 weeks follow-up (Visit 3, Week 6) is (-0.054, 0.141), which is within the bioequivalence limits of -.20 and +.20. The test and reference products also demonstrate superiority over Placebo group at Visit 3. See the FDA statistical review for details.

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

Bioequivalence Analyses based on the evaluable population

Parameter	Test*	Reference	The 90% CI for the Test and Reference	Is the 90% CI within (-20% , 20%)?
Therapeutic Cure at visit 3	***50% (83/165)***	***46% (73/159)***	***(-5.4 , 14.1)***	***YES***
Clinical Cure at visit 3	64% (105/165)	63% (100/159)	(-8.7 , 10.2)	YES
Mycological Cure at visit 3	78% (128/165)	71% (113/159)	(-2.1 , 15.1)	YES
Therapeutic Cure at visit 2	48% (79/165)	51% (81/159)	(-12.8 , 6.7)	YES
Clinical Cure at visit 2	67% (110/165)	67% (107/159)	(-9.8 , 8.6)	YES
Mycological Cure at visit 2	73% (121/165)	73% (116/159)	(-8.3 , 9.1)	YES

Confidence interval calculated using Wald's method with Yates' continuity correction.
*Excluded one patient (#226) based on this reviewer's comment above.

Efficacy Analyses based on the MITT population

Parameter	Treatment arm			p-value	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Therapeutic Cure at visit 3	***45% (84/186)***	***41% (76/187)***	***16% (14/89)***	***< 0.001***	***< 0.001***
Clinical Cure at visit 3	58% (107/186)	57% (106/187)	43% (38/89)	0.03	0.04
Mycological Cure at visit 3	69% (129/186)	63% (118/187)	28% (25/89)	< 0.001	< 0.001
Therapeutic Cure at visit 2	43% (80/186)	45% (84/187)	29% (26/89)	0.03	0.01
Clinical Cure at visit 2	60% (112/186)	60% (112/187)	64% (57/89)	0.60	0.60
Mycological Cure at visit 2	66% (122/186)	65% (121/187)	39% (35/89)	< 0.001	< 0.001

p-values were derived from the 2-sided Fisher's exact test.

VII. Formulation

Taro's formulation

Component	% w/w	ANDA Batch kg	Scale-up Batch kg	Function
Ciclopirox Olamine, USP	1.0*			Active ingredient
Benzyl Alcohol, NF	1.0			Preservative
Cetyl Alcohol, NF				
Cocamide DEA, Taro				
Lactic Acid, USP				
Mineral Oil, USP				
Myristyl Alcohol, NF				
2-Octyldodecanol, NF				
Polysorbate 60, NF				
Purified Water, USP				
Sorbitan Monostearate, NF				
Stearyl Alcohol, NF				
Total	100.0			

*equivalent to 0.77% ciclopirox; Per OGD Chemist review #1

RLD

Ingredient	*Original formulation Quantity Mg	**Revised formulation Quantity Mg
Ciclopirox olamine		
Benzyl alcohol		
2-Octyldodecanol		
**Mineral oil, USP		
Stearyl alcohol		
Cetyl alcohol		
Myristyl alcohol		
Polysorbate 60		
Sorbitan Monostearate		
**Cocomide DEA		
Lactic acid		
Purified water, USP		
Total		

*Per original medical review (NDA 18-748)

**The RLD formulation was revised (8/17/01) to 1) delete inactive ingredient, cocamide DEA with [redacted] and 2) substitute light mineral oil for mineral oil. See NDA Chemist review for details.

Per annual report of NDA 18-748 (12/28/01-11/30/02), all qualitative components are consistent with the revised formulation (without cocamide DEA). In this annual report, no quantitative information was provided.

Reviewer's Comment: *The original reference product was reformulated by deleting inactive ingredient, cocamide DEA, [redacted] because cocamide DEA was thought to cause [redacted] in the reference product.*

The test formulation is qualitatively the same as original formulation of the reference product prior to reformulation.

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 76-790 demonstrate that Taro Pharmaceuticals Inc.'s Ciclopirox Olamine Cream, 0.77%, is bioequivalent to the reference listed drug, Loprox® 0.77 Cream, 0.77%. The FDA statistical review confirms that the 90% CI of the proportional difference in therapeutic cure rates between the test and reference products at the 2 weeks follow-up visit (Visit 3, Week 6) is within (-.20,+.20). The test and reference products also demonstrate superiority over Placebo arm at Visit 3.

B. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 76-790, using the primary endpoint of therapeutic cure rates at the 2 weeks follow-up visit (Visit 3, Week 6), are adequate to demonstrate bioequivalence of Taro Pharmaceuticals Inc.'s Ciclopirox Olamine Cream, 0.77%, with the reference listed drug, Medicis' Loprox® Cream, 0.77%. Both active treatments demonstrated superiority over the Placebo arm at Visit 3.

Please note that patients were considered mycological cure if both KOH and fungal culture results were negative at Week 6 only.

Carol Y. Kim

3/28/05

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

Date

Dena R. Hixon MD

3/28/05

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

Date

Dale P. Conner

3/29/05

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

Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-790 APPLICANT:Taro Pharmaceuticals, Inc.

DRUG PRODUCT: Ciclopirox Cream, 0.77%

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

The data submitted to ANDA 76-790, using the primary endpoint of therapeutic cure rates at the 2 weeks follow-up visit (Visit 3, Week 6), are adequate to demonstrate bioequivalence of Taro Pharmaceuticals Inc.'s Ciclopirox Olamine Cream, 0.77%, with the reference listed drug, Medicis' Loprox® Cream, 0.77%. Both active treatments demonstrated superiority over the Placebo arm at Visit 3.

> Please note that patients were considered mycological cure if both KOH and fungal culture results were negative at Week 6 only.

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

Sincerely yours,

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

ANDA 76-790
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ C.Kim
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/C. Kim CK 3/28/05
HFD-600/D. Hixon DRH 1/28/05
HFD-650/D. Conner NMZ 3/29/05

BIOEQUIVALENCY - ACCEPTABLE

submission dates:
June 30, 2003
October 21, 2004 (dataset)

1. Bioequivalence Study (STU); June 30, 2003 — **Strengths: 0.77%** **Outcome: AC**

2. Study Amendment (STA); — **Strengths: 0.77%** **Outcome: AC**

   October 21, 2004 (dataset)

Please note: This review should close the BCE and BST assignments.

Outcome Decisions: **AC** - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

MAR 29 2005

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # : 76-790 **SPONSOR : Taro**

DRUG AND DOSAGE FORM : Ciclopirox Cream, 0.77%

STRENGTH(S) : 0.77%

TYPES OF STUDIES : Clinical Endpoints

CLINICAL STUDY SITE(S) : Dr. _____ office in _____

STUDY SUMMARY: Study is acceptable.

DSI INSPECTION STATUS

Inspection needed: **YES / NO**	**Inspection report: N/A**	**Inspection results: N/A**
First Generic _____	**Inspection requested: (date)**	
New facility _____	**Inspection completed: (date)**	
For cause _____		
other _____		

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

INITIAL : Carol Y. Kim **DATE :** 3/28/05

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

INITIAL : DRH **DATE :** 3/28/05

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

INITIAL : Dale Conner **DATE :** 3/29/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

STATISTICAL REVIEW

Statistical Review

ANDA 76-790
Drug Product: Ciclopirox Olamine Cream, USP, 0.77% (as ciclopirox)
Sponsor: Taro Pharmaceuticals USA.
Reference Listed Drug: Loprox® Ciclopirox, Cream, 0.77% (NDA 18-748).

Submission dates: 6/30/03, 10/21/04.

Reviewer: Mohamed Moustapha, QMRS/OB/CDER
Clinical Reviewer: Carol Kim, Pharm.D. , OGD/CDER, 12/15/2004.

Remark: The data sets used in this analysis were received in the EDR on October, 21, 2004.

Objectives of the study

The objectives of the study were to demonstrate comparable safety and efficacy of Taro 's Ciclopirox Olamine Cream, USP, 0.77% (Test product) to Medicis' Loprox® Ciclopirox, Cream, 0.77% (Reference product) in the treatment of tinea pedis in order to establish bioequivalence, and to show the superiority of the active treatments over that of Taro's Vehicle (Vehicle).

Study Design

This was a 3 arm parallel-group, double-blind, randomized, placebo-controlled, single-center study to evaluate the safety, efficacy and clinical equivalence of Taro's Ciclopirox (Test product) to Loprox® Ciclopirox, Cream (Reference product) in subjects diagnosed with tinea pedis.

A total of 824 subjects were enrolled and randomly assigned to one of the three treatment groups in a ratio of 2:2:1 (Test: Reference: Vehicle). Subjects diagnosed with Tinea Pedis were enrolled in the study as follow; 186 in the Test group, 187 in the Reference group, and 89 in the Vehicle group. The study was designed to have each subject performing 3 visits. Visit 1 for screening prior to the first dose (Day 1), visit 2 at the end-of-treatment (Day 28), and a follow-up's visit (Day 42) for clinical endpoint evaluations.

Outcome Variables

Primary Endpoint:

The primary endpoint used to assess efficacy and equivalence is the dichotomized (Success / Failure) Therapeutic Cure rate at visit 3 (Day 39 to 45). A patient was classified as a Therapeutic success if he/she had both of the following:

- Clinical Cure
- Mycological Cure

A patient was defined as a Clinical Cure if he/she had the following:

- Total Signs and Symptoms score (Sum of the six Scores) of 2 or less at visit 3

A patient was defined as a Mycological Cure if he/she had the following:

- Negative KOH
- Negative Culture for tinea pedis

Secondary Endpoints:

Per the OGD Medical reviewer's comments the following variables should be considered secondary endpoints:

- Therapeutic Cure rate at visit 2
- Clinical Cure at visits 2 and 3
- Mycological Cure at visits 2 and 3

The sponsor combined mycological results from both visits 2 and 3 for evaluation of a mycological cure. The OGD's Clinical Reviewer stated that for the primary endpoint evaluation, mycological results from only visit 3 (Week 6) should be analyzed.

The following Signs and Symptoms were to be evaluated for their presence and severity:

Investigator's evaluation

- erythema
- scaling (desquamation)
- fissuring
- bullae

Patient's evaluation Scale

Itching
Burning

Severity scale was defined as follows:

0 = none
1 = mild
2 = moderate
3 = moderately severe
4 = severe or extensive

Analysis Populations

Two populations will be evaluated for efficacy and equivalence:

- Modified-Intent-to-Treat population (MITT) –Includes all randomized subjects who met the inclusion/exclusion criteria, who were diagnosed with tinea pedis, received at least one dose of study medication, and returned for at least one post-baseline visit evaluation. This population is the primary population for efficacy analysis.

- Per Protocol population (PP) –Includes all randomized subjects who met all inclusion/exclusion criteria, who were diagnosed with tinea pedis, complied with the minimum treatment course, returned to the study site for visit 2 and 3 within the specified window, and did not have any protocol violations. The Per Protocol population is the primary population for bioequivalence analysis of the Test and the Reference products.

Statistical Analysis Methods

Efficacy Analysis

For the superiority of each active treatment over the Vehicle, the Therapeutic Cure rates in the MITT population at visit 3 were used. In addition, per the OGD Medical reviewer's comments, additional analyses based on secondary endpoints were conducted.

Tests for superiority of each active treatment over the Vehicle were conducted using two-sided Fisher's exact test at the 5% level of significance. The primary analysis was based on the MITT population and the Last Observation Carried Forward (LOCF) approach was used to impute for missing data in the MITT population. However a subject who did not have a post-baseline visit evaluation was excluded from analyses.

Equivalence Analysis

The standard method in OGD to Test for clinical equivalence for binary outcomes is based on the 90% confidence interval for the difference in success rates. The interval was calculated using Wald's method with Yate's continuity correction. Bioequivalence was established if this 90% confidence interval of the difference in the Therapeutic Cure rates between the Test and Reference groups at visit 3 was contained within the interval [–20%, 20%]. The analysis in the PP population was considered primary.

The null hypothesis to be tested was defined as follow:

H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$, versus, H_A: $-.20 \leq p_T - p_R \leq .20$, where:

p_T = Therapeutic Cure rate of the Test product, p_R = Therapeutic Cure rate of the Reference product.

Let n_T = Sample size of the Test product, n_R = Sample size of the Reference product.

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

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

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

We reject H_0 if $L \geq -.20$ and $U \leq .20$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

Statistical Analysis Results

Demographic characteristics

A total of 986 patients were initially screened, one hundred sixty (160) patients were considered as screening failures (violation of inclusion/exclusion criteria) at baseline. Of 826 patients eligible for enrollment, a total of 462 patients were included in the ITT population; 186 in the test, 187 in the reference, and 89 in the vehicle groups, respectively. Three hundred sixty four (364) patients were excluded from the ITT population due to negative baseline culture or

contaminated culture specimen. Of the total 462 MITT populations, 66.2% (306) are White, 11% (51) are Black, 20.3% (94) are Hispanic, and 2.4% (11) are of other ethnicity. Three hundred sixty one patients are Male and 101 are Female, however there was no statistically significant gender difference across treatment groups.

Table 1 describes the demographic characteristics for the MITT population.

Overall, there was no statistically significant difference across treatment groups in the demographic characteristics; Gender, or Race, where p-values were, 0.283, and 0.489.

Table 1- Demographic characteristics of the MITT population

Age (in Years)	Test (N = 186)	Reference (N = 187)	Vehicle (N = 89)	p-Value
MAX	82	79	81	
MEAN	40	40	39	
MIN	19	19	18	0.25 [2]
N	186	187	89	
STD	12	13	13	
Race				
Caucasian	123 (26.6%)	125 (27.1%)	58 (12.6%)	
Black	19 (4.1%)	22 (4.8%)	10 (2.2%)	0.99 [1]
Hispanic	39 (8.4%)	36 (7.8%)	19 (4.1%)	
Others	5 (1.1%)	4 (0.9%)	2 (0.4%)	
Gender Male	148 (32.0%)	143 (31.0%)	70 (15.2%)	0.76 [1]
Female	38 (8.2%)	44 (9.5%)	19 (4.1%)	

[2] p-value for treatment comparisons from ANOVA model with treatment as covariate.
[1] p-value for treatment comparisons from Cochran-Mantel-Haenszel Test for general association.

Baseline characteristics

The sponsor stated (Table 2 below), that the MITT population consisted of 186 subjects assigned to the Test product, 187 subjects assigned to the Reference product, and 89 subjects in the Vehicle. The PP population included 166 patients in the Test product group, 159 in the Reference product group, and 82 in the Vehicle group. However patient # 126 (in the Test group) was excluded from the PP population based on the OGD's Medical reviewer's comments.

Signs and Symptoms as defined in a previous section (page 2), were compared across treatment groups at baseline. Erythema, scaling (desquamation), fissuring, bullae, Burning, and Itching were found to be comparable at baseline across the three treatment groups in the MITT population. There were no statistically significant differences between treatments in the MITT population with regard to ratings for erythema (p=0.83), scaling (p=0.42), fissuring (p=0.97), Bullae (p=0.27), Itching (p=0.48), or Burning (p=0.70).

Table 2. Population distribution

Population	Test (N = 186)	Reference (N = 187)	Vehicle (N = 89)	Total (N = 462)
Subjects Enrolled	332 (100%)	331 (100%)	161 (100%)	824 (100%)
Patients Excluded from MITT	146 (44%)	144 (44%)	72 (45%)	362 (44%)
Total Patients in the MITT	186 (56%)	187 (56%)	89 (55%)	462 (56%)
Patients Excluded from PP	167 (50%)	172 (52%)	79 (49%)	418 (51%)
Total Patients in the PP	165 (50%)	159 (48%)	82 (51%)	406 (49%)

Table 3. Population Analysis distribution (reviewer's analysis)

Parameter		Test (N = 186)	Reference (N = 187)	Vehicle (N = 89)	Total (N = 462)	p-value [1]
Erythma	None	0	0	0	0	
	Mild	91	93	44	228	
	Moderate	94	94	45	233	0.83
	Moderately severe	1	0	0	1	
	Severe	0	0	0	0	
Scaling	None	0	0	0	0	
	Mild	9	7	8	24	
	Moderate	124	118	51	293	0.42
	Moderately severe	52	60	30	142	
	Severe	1	2	0	3	
Fissuring	None	66	64	31	161	
	Mild	112	117	54	283	
	Moderate	8	6	4	18	0.97
	Moderately severe	0	0	0	0	
	Severe	0	0	0	0	
Bullae	None	183	185	87	455	
	Mild	1	2	1	4	
	Moderate	2	0	0	2	0.27
	Moderately severe	0	0	1	1	
	Severe	0	0	0	0	
Itching	None	0	1	1	2	
	Mild	49	35	24	108	
	Moderate	56	65	31	152	0.48
	Moderately severe	61	69	24	154	
	Severe	20	17	9	46	
Burning	None	177	172	84	433	
	Mild	6	6	3	15	
	Moderate	2	7	1	10	0.70
	Moderately severe	1	1	1	3	
	Severe	0	1	0	1	

[1] p-value for treatment comparisons from the Cochran-Armitage Test for trend.

Efficacy analyses

The efficacy analyses based on the Therapeutic Cure rate at visit 3 (primary endpoint) in the MITT population showed evidence of superiority of the Test and Reference products over the Vehicle. The Tests for comparing the Test and the Reference product to the Vehicle were statistically significant (p-Value < 0.001). In addition, comparisons based on secondary endpoints such as, Therapeutic Cure at visit 2, Clinical Cure at visit 3, Mycological Cure at visits 2 and 3 showed the Test and the Reference products were better than Vehicle. Table 4 summarizes the efficacy results based on the primary and secondary endpoints in the MITT population. Only Clinical Cure at visit 2 failed to show superiority of the Test and Reference products over the Vehicle (p-values = 0.60).

Table 4 - Efficacy Analyses based on the MITT population

Parameter	Treatment arm			p-value	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Therapeutic Cure at visit 3	*45% (84/186)*	*41% (76/187)*	*16% (14/89)*	*< 0.001*	*< 0.001*
Clinical Cure at visit 3	58% (107/186)	57% (106/187)	43% (38/89)	0.03	0.04
Mycological Cure at visit 3	69% (129/186)	63% (118/187)	28% (25/89)	< 0.001	< 0.001
Therapeutic Cure at visit 2	43% (80/186)	45% (84/187)	29% (26/89)	0.03	0.01
Clinical Cure at visit 2	60% (112/186)	60% (112/187)	64% (57/89)	0.60	0.60
Mycological Cure at visit 2	66% (122/186)	65% (121/187)	39% (35/89)	< 0.001	< 0.001

p-values were derived from the 2-sided Fisher's exact test.

The Test and Reference products were found to be clinically equivalent for the Therapeutic Cure rate (primary endpoint) in the PP population. In addition, the clinical equivalence test based on secondary endpoints such as Therapeutic Cure at visit 2, Clinical Cure at visits 2 and 3, and Mycological Cure at visits 2 and 3 provided supportive evidence of the clinical equivalence of the Test and the Reference products. Table 5 summarizes the clinical equivalence results.
Table 6 - Bioequivalence Analyses based on the PP population

Parameter	Test	Reference	The 90% CI for the Test and Reference	Is the 90% CI within (-20% , 20%)?
Therapeutic Cure at visit 3	***50% (83/165)***	***46% (73/159)***	***(-5.4 , 14.1)***	***YES***
Clinical Cure at visit 3	64% (105/165)	63% (100/159)	(-8.7 , 10.2)	YES
Mycological Cure at visit 3	78% (128/165)	71% (113/159)	(-2.1 , 15.1)	YES
Therapeutic Cure at visit 2	48% (79/165)	51% (81/159)	(-12.8 , 6.7)	YES
Clinical Cure at visit 2	67% (110/165)	67% (107/159)	(-9.8 , 8.6)	YES
Mycological Cure at visit 2	73% (121/165)	73% (116/159)	(-8.3 , 9.1)	YES

Confidence interval calculated using Wald's method with Yates' continuity correction.

Comments on the Sponsor's Analyses

The Sponsor's primary efficacy variable was Therapeutic Cure rate at the Test-of-Cure visit (visit 3, between day 39 and 45). Based on the sponsor's statistical analysis using 90% confidence intervals, the study demonstrates that the difference in the Therapeutic Cure rates between the Test and the Reference products is within [-.20, +.20] .

The sponsor's analyses, while they reach a similar conclusion with regard to bioequivalence for the primary endpoint, were based on a different PP population than that of this reviewer.

Table 7: **Primary Efficacy Analysis: Therapeutic Cure[1] Rate at Visits 2 and 3 combined (per sponsor)**

Parameter	TARO	RLD	90% C.I. for Bioequivalence of Taro's product to Loprox®		
Per-Protocol Patients					
Visit 2 and 3 combined	(N=166)	(N=159)			
Therapeutic Cure	60 (36%)	59 (37%)	(-10.4%, 8.4%)		
Clinical Cure	105 (63%)	100 (63%)	(-9.1%, 9.8%)		
Mycological Cure	95 (57%)	90 (57%)	(-9.0%, 10.3%)		
Intent-to-Treat Patients					
	TARO	RLD	Vehicle	P-Value (2-sided cc Z-test)	
Visit 2 and 3 combined	(N=186)	(N=187)	(N=89)	T vs. Vehicle	Ref vs. Vehicle
Therapeutic Cure	60 (32%)	60 (32%)	9 (10%)	<0.001	<0.001
Clinical Cure	106 (57%)	103 (55%)	37 (42%)	0.02	0.05
Mycological Cure	96 (52%)	94 (50%)	18 (20%)	<0.001	<0.001

[1] Mycological cure defined as culture and KOH negative at 4 weeks after baseline. Clinical cure defined as any sign or symptom that was 1 or 2 at baseline should be 0; and any s/s that was a 3 should be a 1 or 0 (discharge could be 0 or 1). Therapeutic cure defined as giving both a clinical and mycological cure. Patients missing visit 2 designated as mycological, clinical and therapeutic failures.

According to the sponsor's analysis, the Test and Reference products were both statistically significantly superior over the Vehicle ($p < 0.001$) for the Therapeutic cure rate. In addition, based on the Therapeutic cure rate at visit 3 (primary endpoint); the sponsor stated that the equivalence Test met the 90% CI criteria within [-.20, +.20] for both the PP and MITT populations.

Conclusion

Efficacy:

Our analysis showed that the Test and Reference products were both statistically significantly better than Vehicle in the treatment of tinea pedis for Therapeutic Cure at visit 3 (primary endpoint) in the MITT population. Additionally, analyses based on secondary endpoints showed the superiority of both the Test and Reference products over the Vehicle in the MITT population, except for the Clinical Cure at visit 2.

Equivalence: The Test and Reference products were found to be clinically equivalent for all variables (primary and secondary endpoints) in the PP population.

3/31/05

Mohamed Moustapha
Mathematical Statistician, QMR

Donald J. Schuirmann 3/31/05

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado 3/31/05

Stella G. Machado, Ph.D.
Director, QMR

cc: Original ANDA 76-790
HFD-600
Dena Hixon, Carol Kim, Krista Scardina
HFD-705
Stella Machado, Donald J. Schuirmann, Mohamed Moustapha
HFD-705 QMR Chron.

This Review Includes 8 Pages, 03/23/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-790 Applicant Taro Pharmaceuticals IPC
Drug Ciclopirox Cream Strength(s) 0.77%

APPROVAL **TENTATIVE APPROVAL** **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** **OTHER**

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 21 Sept 04 Initials MAS	Date_____ Initials_____

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)
Determ. of Involvement? Yes No
Pediatric Exclusivity System
RLD = NDA#_____
Patent/Exclusivity Certification: (Yes) No
Date Checked _____
If Para. IV Certification- did applicant
Nothing Submitted
Notify patent holder/NDA holder Yes No
Written request issued
Was applicant sued w/in 45 days: Yes No
Study Submitted
Has case been settled: Yes No Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes No
Type of Letter:
Comments: No patents/exclusivities: eligible for full approval

P 3

2. Project Manager, _____ Team____ Review Support Branch	Date 4/8/05 Initials D	Date_____ Initials_____

Original Rec'd date 6/30/03
Date Acceptable for Filing 6/30/03
Patent Certification (type) 11 7/11/03
Date Patent/Exclus.expires _____
Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)
First Generic Yes (No)
Altana 76-435 Ap'd 12/29/04 JMC

EER Status Pending (Acceptable) OAI
Date of EER Status 2/3/04
Date of Office Bio Review 3/29/05
Date of Labeling Approv. Sum 3/5/05
Labeling Acceptable Email Rec'd Yes No
Labeling Acceptable Email filed Yes No
Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes No
MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed (Yes) No
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted Rejected Pending
Previously reviewed and tentatively approved Date _____
Previously reviewed and CGMP def. /NA Minor issued Date _____
Comments:

Modified-release dosage form: Yes No
Interim Dissol. Specs in AP Ltr: Yes

3. David Read **(PP IVs Only)** Pre-MMA Language included OGD Regulatory Counsel, Post-MMA Language Included Comments:		Date _____ Initials_____

4. Div. Dir./~~Deputy DIR~~. Chemistry Div. I ~~II OR III~~ Comments:		Date 4/12/05 Initials 12/5

The comunication is satisfactory

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only**
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
Altana 76-435 Approved 2/29/04
N/A
RLD = Loprox Cream NDA - 18748-001
Date —
Initials —

6. Vacant
Deputy Dir., DLPS
Date
Initials

7. Peter Rickman
Director, DLPS
Date CK 4/12/05
Initials
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments:
There are no patents or unexpired exclusivities for this product.
EES is acceptable 2/3/04 - both API supplier + finished dose manufacturer present.
OR Bro is acceptable 3/29/05 based on results from the clinical endpoint study
NO DSE inspection needed - Acceptable DSI history 3/29/05 - D. Conner
Taro Pharmaceuticals filed a paragraph II certification to Application 76780.
There are no patents or exclusivities active.
Labeling acceptable 3/23/04 - J. Grace Labeling signoff 4/8/05
CMC acceptable 4/9/05 - J. FAN

8. Robert L. West
Deputy Director, OGD
2nd Generic good for full AP
Date 4/12/05
Initials
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments:
MV is not required - USP product
micro review not required
ANDA is ready for Full Approval

9. Gary Buehler
Director, OGD
Comments:
4/12/05 GB
Date 4/12/05
Initials CK
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team 3 - Ann Vu
Review Support Branch
Date 4/13/05
Initials
4/12/05 Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
5:45p Time notified of approval by phone 5:47 Time approval letter faxed
HDA Notification:
4/13/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/13/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-790

CORRESPONDENCE

ANDA 76-790

AUG 11 2003

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

Dear Madam:

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

NAME OF DRUG: Ciclopirox Olamine Cream USP, 0.77%

DATE OF APPLICATION: June 30, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 1, 2003

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

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

Should you have questions concerning this application, contact:

Ann Vu
Project Manager
(301) 827-5848

Sincerely yours,

Gregory K. Davis for

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

ANDA 76-790
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis,Chief, RSB Carmelina A.B.C. date 04-Aug-03
HFD-615/PPatel,CSO [signature] date 8/4/03
Word File V:\Firmsam\Taro\ltrs&rev\76790.ACK
F/T
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

February 17, 2004

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

Taro Pharmaceuticals U.S.A., Inc.

ORIG AMENDMENT
N/Am.
FPL

Re: **ANDA 76-790– Minor Amendment**
Ciclopirox Olamine Cream USP, 0.77% (as ciclopirox)

Dear Ms. Vu:

Reference is made to the Taro Pharmaceuticals U.S.A. Inc.'s Abbreviated New Drug Application for the above referenced product submitted on June 30, 2003.
Reference is also made to the Agency's letter of December 9, 2003 concerning the chemistry deficiencies pertaining to this application.

For ease of review the Agency's comments presented in the Minor Amendment Letter have been provided below and are followed by our response.

A. Deficiencies:

[redacted]

RECEIVED
FEB 18 2004
OGD/CDER

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

2/17/2004 TARO LETTER

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

Comment 1
The bioequivalence and labeling sections of your application are under review and you will be notified separately of any deficiencies.

Response
Acknowledged.

Comment 2
The USP methods for the drug substance and product are the regulatory methods and will prevail in the event of a dispute.

Response
Acknowledged.

Comment 3
A satisfactory compliance evaluation for each of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of approval.

Response
Acknowledged.

Comment 4
Please provide all available updated drug product long-term room temperature stability data for our evaluation.

Response
Updated room temperature stability data (up to 12 months for the 15 g, 30 g and 90 g sizes; [redacted]) is provided in Attachment 8 (supplementary pages 46-59). Please note that the product [redacted] Consequently, Taro wishes to withdraw the [redacted] size from this application. Twelve final printed insert labels are provided in Attachment 9 (plastic folder) to reflect this change. Also provided is a side by side comparison (supplementary pages 60-64) indicating the only change to the previously submitted insert is the removal of the [redacted] package size.

This completes our response to the Agency's Minor Amendment Letter of December 9, 2003. If there are any questions regarding this amendment, or if additional information is required, please contact the undersigned at:

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

Sincerely yours,

for K. Rao

Kalpana Rao
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

March 12, 2004

TARO

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
FPL N|AF

Re: ANDA 76-790
Ciclopirox Olamine Cream USP, 0.77%
Labeling Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Ciclopirox Olamine Cream USP, 0.77% submitted June 30, 2003, and to the labeling deficiency letter from the Agency on March 8, 2004 in which the following was noted:

1. *GENERAL COMMENTS [ALL LABELING]*
   a. *Delete "————— " following the established name "Ciclopirox Olamine Cream USP, 0.77%".*
   b. *Because your stability studies are conducted at 25 ± 2°C, 60% ± 5% RH, revise your storage temperature to read "Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]".*
2. *CONTAINER — 15 g, 30 g and 90 g)*
3. *CARTON (15 g, 30 g and 90 g)*
   See GENERAL COMMENTS
4. *INSERT*
   See GENERAL COMMENTS

Please revise your labels and labeling, as instructed above, and submit 12 final printed copies for approval.

Response:
We have revised our labels and package insert as per the Agency's recommendations and enclosed please find:

- **12 - Final Printed** — **tube labels:** mistake on Taro's. TARO withdrew the — size as of Feb. 17, 2004 submission.
- **12 - Final Printed 15 g tube and carton labels**
- **12 - Final Printed 30 g tube and carton labels**
- **12 - Final Printed 90 g tube and carton labels**
- **12 - Final Printed Package Inserts**

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MAR 15 2004
OGD/CDER

In addition, and in accordance with 21 CFR314.94(a)(8)(iv), we have included a side-by-side comparison of our previously submitted package insert with our currently submitted package insert.

This concludes our response to the Agency's labeling deficiency letter of March 8, 2004.

Sincerely,

3/12/04

Kalpana Rao
Vice President, Regulatory Affairs
Taro Pharmaceuticals U.S.A., Inc.

APPEARS THIS WAY
ON ORIGINAL

March 23, 2004

TARO

Taro Pharmaceuticals U.S.A., Inc.

MC

Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 76-790
Ciclopirox Olamine Cream USP, 0.77%
Labeling Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Ciclopirox Olamine Cream USP, 0.77% submitted June 30, 2003, and to our Labeling Amendment dated March 12, 2004 as well as the telephone call from Beverly Weitzman of the Agency on March 22, 2004 in which the following was noted:

Comment:
You have removed the ——— size from your chemistry section of the ANDA, however you submitted final printed labeling (FPL) on March 12, 2004. Please comment.

Response:
At this time, Taro would like to withdraw all reference to the ——————— tube size including all labeling. The FPL for the ——— tube that was submitted in the March 12, 2004 Labeling Amendment was an error on our part and we regret any inconvenience this may have caused.

This concludes our response to the Agency's telephone call of March 22, 2004.

Sincerely,

3/23/04

Kalpana Rao
Vice President, Regulatory Affairs
Taro Pharmaceuticals U.S.A., Inc.

RECEIVED
MAR 2 4 2004
OGD/CDER

June 2, 2004

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

ORIG AMENDMENT
N/AM

Re: **ANDA 76-790– Minor Amendment**
Ciclopirox Olamine Cream USP, 0.77% (as ciclopirox)

Dear Ms. Vu:

Reference is made to the Taro Pharmaceuticals U.S.A. Inc.'s Abbreviated New Drug Application for the above referenced product submitted on June 30, 2003 and the minor amendment dated February 17, 2004.

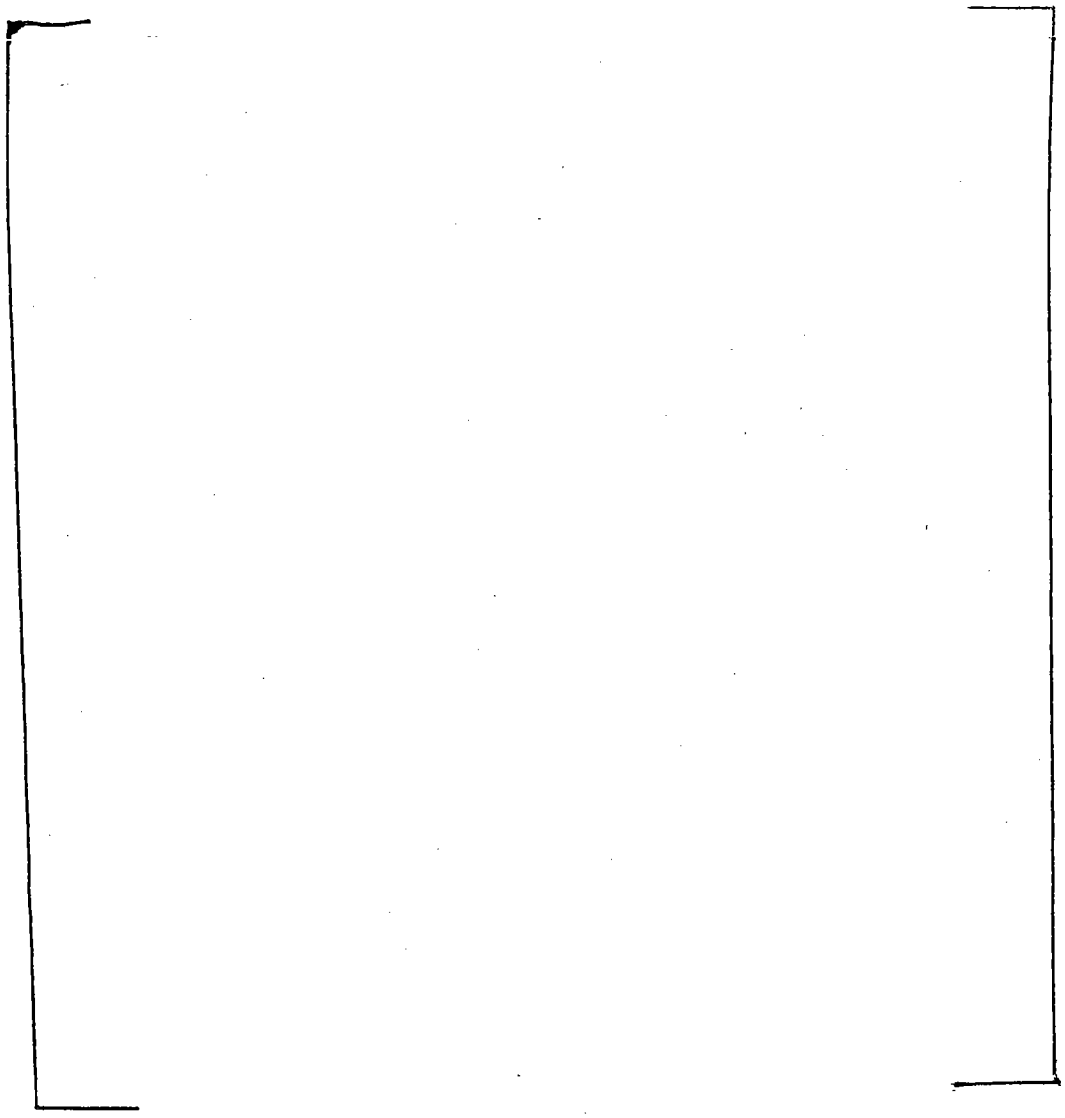
Reference is also made to the Agency's letter of May 7, 2004 concerning the chemistry deficiencies pertaining to this application.

For ease of review the Agency's comments presented in the Minor Amendment Letter have been provided below and are followed by our response.

A. Deficiencies:

RECEIVED
JUN 0 3 2004
OGD/CDER

Taro Pharmaceuticals Inc.
130 East Drive, Brampton, Ontario L6T 1C1 Tel: 905-791-8276 1-800-268-1975 Fax: 905-791-4473 www.taro.ca



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

Comment 1
The bioequivalence section of your application is under review and you will be notified separately of any deficiencies.

Response
Acknowledged.

Comment 2
Please provide all available updated drug product long-term room temperature stability data for our evaluation.

Response

Updated room temperature stability data (up to 12 months) was provided in the February 17, 2004 response to the agency's minor amendment letter dated December 9, 2003. The 18 month samples are due to be tested June 18, 2004. The 18 month stability data will be submitted to FDA when available.

This completes our response to the Agency's Minor Amendment Letter of May 7, 2004. If there are any questions regarding this amendment, or if additional information is required, please contact the undersigned at:

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

Sincerely yours,

Kalpana Rao
Vice President, Regulatory Affairs

MEMORANDUM

To: **ANDA 76-790**

Drug: **Ciclopirox Olamine Cream USP, 0.77% (as ciclopirox)**

Sponsor: **Taro Pharmaceuticals USA., Inc.**
Kalpana Rao, Vice President, Regulatory Affairs
PH: (914) 345-9001 ext. 6298
FAX: (914) 593-0078

From: **Carol Y. Kim, Pharm.D.** 10/15/04
Clinical Reviewer
Office of Generic Drugs
FAX: (301) 827-6363

Dena R. Hixon, MD Dena R. Hixon MD
Associate Director for Medical Affairs
Office of Generic Drugs

Date: **October 15, 2004**
Re: **Request for Information**

In order to complete the review of a bioequivalence study with clinical endpoints for ANDA 76-790 (CPO 0208), please provide the following information:

1. A new SAS data set including line listings of the study outcome (e.g. clinical cure/failure) and patient population (Intent-to-Treat vs. Per Protocol) for each patient. One line summary data set should include the following variables for <u>each patient per visit</u> if data exist:

    - Center/site, patient/subject number, treatment group
    - Intent-to-Treat (ITT) Population (yes/no), reason for exclusion from ITT from week 4 visit (end of treatment), reason for exclusion from ITT from week 6 follow-up visit
    - Per Protocol (PP) Population (yes/no), reason for exclusion from PP from week 4 visit (end of treatment), reason for exclusion from PP from week 6 follow-up visit
    - Race, sex, age
    - Visit number, date of visit, days from baseline visit (initial dose visit)
    - Clinical response (cure/failure) at separate week 4 visit (end of treatment) and at week 6 follow-up visit
    - Mycological response (cure/failure) at separate week 4 visit (end of treatment) and at week 6 follow-up visit
    - Therapeutic cure/failure at separate week 4 (end of treatment) visit and at week 6 follow-up visit

- Severity of individual signs and symptoms
- Mycological results (e.g. KOH and culture)
- Completion of the study (yes/no), date, reason for discontinuation
- Treatment compliance (yes/no), number of doses missed
- Adverse Events

Please provide "define.pdf" with detailed description of code that you use for each variable in the dataset (for example, 0=yes, 1=no for patient population). All SAS transport files should use .xpt as the file extension and should not be compressed.

A separate file for raw data (missing data left blank) and derived data (Last Observation Carried Forward method used) is requested.

2. A summary of patient disposition (accountability) in details as follows:

    a. Total number of patients initially screened per treatment group
    b. Total number of patients failed to meet screening criteria per treatment group and specify reason for screening failure for each patient
    c. Total number of patients with negative KOH result at visit 1 per treatment group
    d. Total number of patients finally enrolled into the study per treatment group
    e. Total number of patients randomized and received the study treatment per treatment group

3. Define treatment compliance criterion that was used in the study. How many doses of the study drug can be missed and considered as treatment compliant?

4. A summary table displaying the frequency of adverse events as follows:
    a. Compare and tabulate overall frequency of adverse events by severity (mild, moderate, and severe) for each treatment group. Tabulate treatment related events versus non-treatment related events.
    b. Compare and tabulate overall frequency of adverse events related to skin and by severity for each treatment group. For example, provide frequency of adverse events reported for burning or irritation at the application site.
    c. Compare and tabulate overall frequency of adverse events related to body system (e.g. headache-# of events, # of patients).

5. Sort concomitant medications used during the study per treatment group and patient number and specify patient population (ITT, PP) for each patient.

6. Provide the study report ("CPO0208") including the summary tables (Table 1 to 12b) and protocol/amendments in electronic format (e.g. PDF file).

TARO
Taro Pharmaceuticals U.S.A., Inc.

October 21, 2004

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

Re: ANDA 76-790
Ciclopirox Olamine Cream USP, 0.77% (as ciclopirox)
Bioequivalence Amendment

Dear Ms. Kim,

Reference is made to Taro Pharmaceuticals Inc.'s Abbreviated New Drug Application submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act Ciclopirox Olamine Cream USP, 0.77% (as ciclopirox), ANDA 76-790. Reference is also made to the Agency's Request for Information dated October 15, 2004, in which the followings were requested:

Request 1:
A new SAS data set including line listings of the study outcome (e.g. clinical cure/failure) and patient population (Intent-to-Treat vs. Per Protocol) for each patient. One line summary data set should include the following variables for each patient per visit if data exist:

- *Center/site, patient/subject number, treatment group*
- *Intent-to-Treat (ITT) Population (yes/no), reason for exclusion from ITT from week 4 visit (end of treatment), reason for exclusion from ITT from week 6 follow-up visit*
- *Per Protocol (PP) Population (yes/no), reason for exclusion from PP from week 4 visit (end of treatment), reason for exclusion from PP from week 6 follow-up visit*
- *Race. sex, age*
- *Visit number, date of visit, days from baseline visit (initial dose visit)*
- *Clinical response (cure/failure) at separate week 4 visit (end of treatment) and at week 6 follow-up visit*
- *Mycological response (cure/failure) at separate week 4 visit (end of treatment) and at week 6 follow-up visit*
- *Therapeutic cure/failure at separate week 4 (end of treatment) visit and at week 6 follow-up visit*
- *Severity of individual signs and symptoms*
- *Mycological results (e.g. KOH and culture)*
- *Completion of the study (yes/no), date, reason for discontinuation*
- *Treatment compliance (yes/no), number of doses missed*
- *Adverse events*

Please provide "define.pdf" with detailed description of code that you use for each variable in the dataset (for example, 0=yes, 1=no for patient population). All SAS transport files should use .xpt as the file extension and should not be compressed.

A separate file for raw data (missing data left blank) and derived data (Last Observation Carried Forward method used) is requested.

Request 2:
A summary of patient disposition (accountability) in details as follows:

a. *Total number of patients initially screened per treatment group*
b. *Total number of patients failed to meet screening criteria per treatment group and specify reason for screening failure for each patient*
c. *Total number of patients with negative KOH result at visit 1 per treatment group*
d. *Total number of patients finally enrolled into the study per treatment group*
e. *Total number of patients randomized and received the study treatment per treatment group*

Request 3:
Define treatment compliance criterion that was used in the study. How many doses of the study drug can be missed and considered as treatment compliant?

Request 4:
A summary table displaying the frequency of adverse events as follows:

a. *Compare and tabulate overall frequency of adverse events by severity (mild, moderate and severe) for each treatment group. Tabulate treatment related events versus non-treatment related events.*
b. *Compare and tabulate overall frequency of adverse events related to skin and by severity for each treatment group. For example, provide frequency of adverse events reported for burning or irritation at the application site.*
c. *Compare and tabulate overall frequency of adverse events related to body system (e.g. headache- # of events, # of patients).*

Request 5:
Sort concomitant medications used during the study per treatment group and patient number and specify patient population (ITT, PP) for each patient.

Request 6:
Provide the study report ("CPO0208") including the summary tables (Table 1 to 12b) and protocol/amendments in electronic format (e.g. PDF file).

Response:
The requested information is provided in SAS and PDF files format on a CD enclosed along with this cover letter.

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confidential commercial

information from

10/21/2004 TARO LETTER

We hope that our response satisfactorily address your request. If there are any questions, or additional information is required, please contact the undersigned at 914-345-9001, ext. 6298.

Sincerely,

10/21/04

Kalpana Rao (U.S. Agent)
Vice-President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL