CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 205181

Name: Butenafine Hydrochloride Cream, 1%

Sponsor: Taro Pharmaceuticals USA

Approval Date: November 16, 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA205181Orig1s000

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Pharm/Tox Review	
Bioequivalence Review(s)	**X**
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Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 205181

ANDA APPROVAL

Taro Pharmaceuticals USA Inc.
3 Skyline Drive
Hawthorne, NY 10532
Attention: Crystal Spinks
Manager, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 4, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Butenafine Hydrochloride Cream, 1%.

Reference is also made to the complete response letter issued by this office on September 28, 2016, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Butenafine Hydrochloride Cream, 1%, to be bioequivalent to the reference listed drug (RLD), Lotrimin Ultra Cream, 1%, of Bayer HealthCare LLC.

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

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Office of Generic Drugs should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Office of Generic Drugs in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. [As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.].

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Heidi Lee

Digitally signed by Heidi Lee
Date: 11/16/2017 10:15:52AM
GUID: 52795fe90009070673e7de063d080d1f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

LABELING


CAP END
OPEN END
MONTEBELLO LENGTH: 3.2812" (83.342mm)
TUBE LENGTH: 3.25" (82.55mm)
Side Seam – Overlap
Side Seam – Overlap
Side Seam – Overlap
5 mm (0.197")
FRONT PANEL 29.924 mm (1.1781")
BACK PANEL 24.248 mm (0.9546")
5 mm (0.197")
FINAL WIDTH 61.343 mm (2.4151")
CENTER LINE
CENTER LINE
Butenafine
Hydrochloride Cream 1%
Antifungal
NDC 51672-2101-8
NET WT 12 g (0.42 oz)
Active ingredient Purpose
Butenafine hydrochloride 1%..... .....Antifungal
Uses • cures most jock itch • relieves itching, burning, cracking, and scaling which accompany this condition
Warnings For external use only.
Do not use • on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections.
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse.
Keep out of reach of children. f swallowed, get medical help or contact a Poison Control Center right away.
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 Made in Canada.
LPK-7032-0 0516-0 35
Directions
• adults and children 12 years and older: • use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • apply once a day to affected skin for 2 weeks or as directed by a doctor • wash hands after each use • children under 12 years: ask a doctor.
Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date.
Store between 20° to 25° C (68° to 77° F).
Questions? Call 1-866-923-4914
N 3 51672 21018 2
L3/4" x 3 1/4" (TU40.2)
0.1875" - 4.762 mm Copy Free Area
Shoulder weld 0.0312" - 0.1969 mm
0.132" - 3.175 mm
0.239" - 5.994 mm Perimeter
0.394" - 10.008 mm
0.2756" - 7 mm Lot and Expiry
Copy Free Area — 0.755" - 19.177 mm

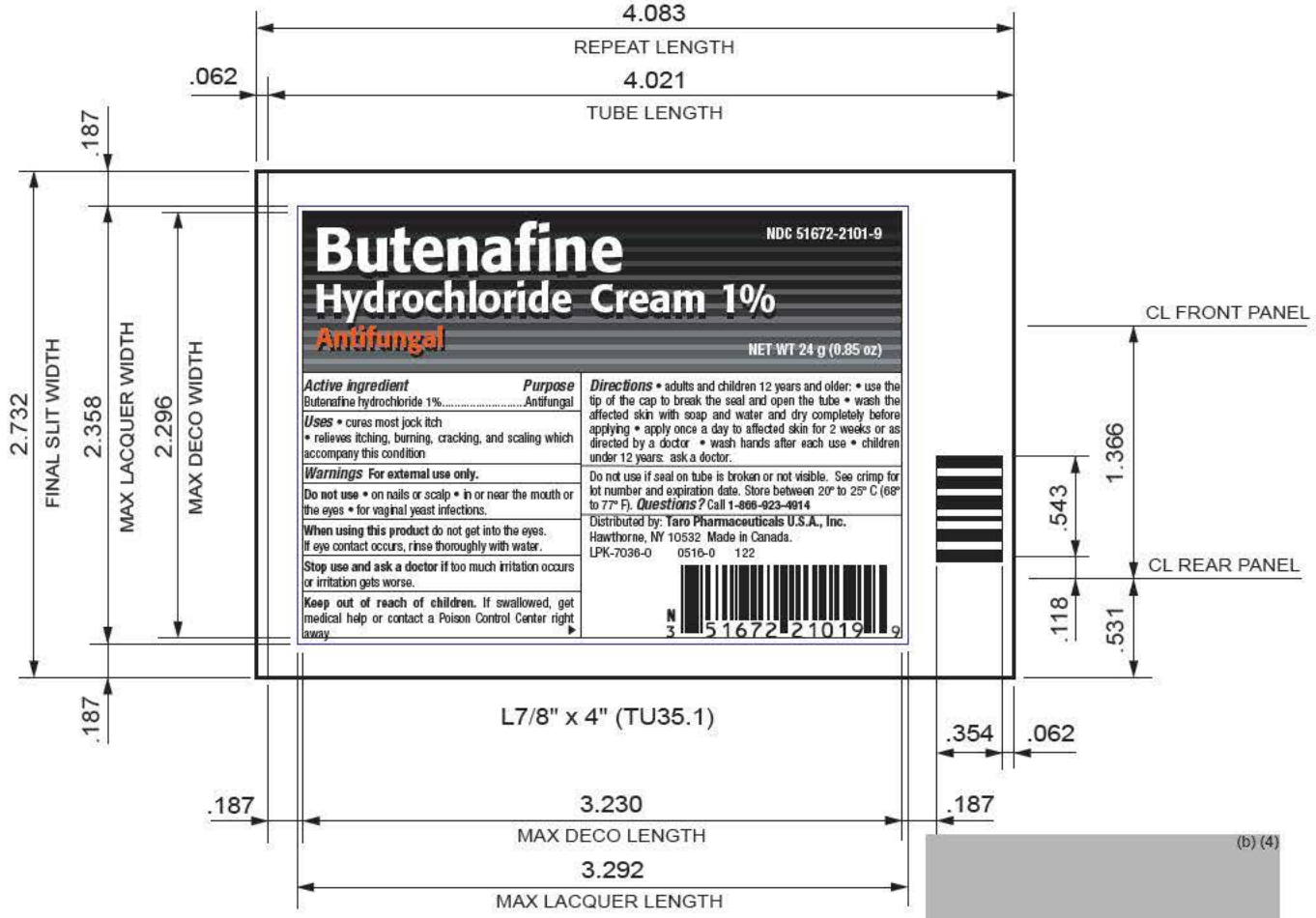
(b) (4)

(b) (4)

TU43.2 - 3/4" x 4 1/4"

(b) (4)

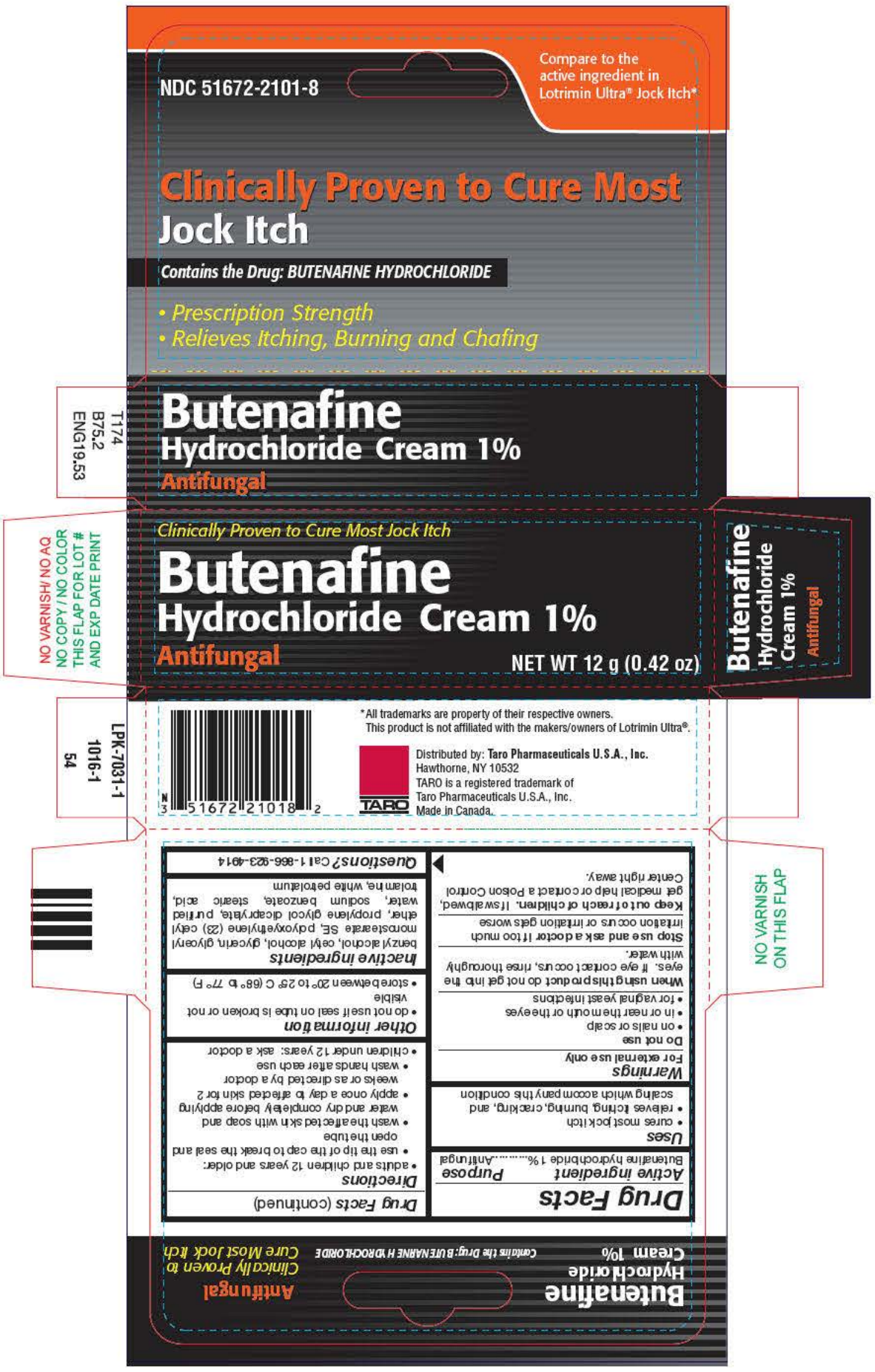
(b) (4)


4.083
REPEAT LENGTH
.062
4.021
TUBE LENGTH
.187
2.732
FINAL SLIT WIDTH
2.358
MAX LACQUER WIDTH
2.296
MAX DECO WIDTH
Butenafine
Hydrochloride Cream 1%
Antifungal
NDC 51672-2101-9
NET WT 24 g (0.85 oz)
Active ingredient
Purpose
Butenafine hydrochloride 1%
Antifungal
Uses • cures most jock itch • relieves itching, burning, cracking, and scaling which accompany this condition
Warnings For external use only.
Do not use • on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections.
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions • adults and children 12 years and older: • use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • apply once a day to affected skin for 2 weeks or as directed by a doctor • wash hands after each use • children under 12 years: ask a doctor.
Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date. Store between 20° to 25° C (68° to 77° F). Questions? Call 1-866-923-4914
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 Made in Canada.
LPK-7036-0 0516-0 122
CL FRONT PANEL
1.366
.543
CL REAR PANEL
.118
.531
L7/8" x 4" (TU35.1)
.354
.062
.187
3.230
MAX DECO LENGTH
.187
3.292
MAX LACQUER LENGTH
(b) (4)
(b) (4)
(b) (4)

TU13.3 - 1" x 4"

(b) (4)

(b) (4)


NDC 51672-2101-8
Compare to the active ingredient in Lotrimin Ultra® Jock Itch*
Clinically Proven to Cure Most Jock Itch
Contains the Drug: BUTENAFINE HYDROCHLORIDE
• Prescription Strength
• Relieves Itching, Burning and Chafing
Butenafine Hydrochloride Cream 1%
Antifungal
Clinically Proven to Cure Most Jock Itch
Butenafine Hydrochloride Cream 1%
Antifungal
NET WT 12 g (0.42 oz)
Butenafine Hydrochloride Cream 1% Antifungal
NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT
T174
B75.2
ENG19.53
LPK-7031-1
1016-1
54
*All trademarks are property of their respective owners.
This product is not affiliated with the makers/owners of Lotrimin Ultra®.
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
TARO is a registered trademark of
Taro Pharmaceuticals U.S.A., Inc.
Made in Canada.
TARO
NO VARNISH ON THIS FLAP
Drug Facts
Active ingredient
Butenafine hydrochloride 1%
Purpose
Antifungal
Uses
• cures most jock itch
• relieves itching, burning, cracking, and scaling which accompany this condition
Warnings
For external use only
Do not use
• on nails or scalp
• in or near the mouth or the eyes
• for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Questions? Call 1-866-923-4914
Drug Facts (continued)
Directions
• adults and children 12 years and older:
• use the tip of the cap to break the seal and open the tube
• wash the affected skin with soap and water and dry completely before applying
• apply once a day to affected skin for 2 weeks or as directed by a doctor
• wash hands after each use
• children under 12 years: ask a doctor
Other information
• do not use if seal on tube is broken or not visible
• store between 20° to 25° C (68° to 77° F)
Inactive ingredients
benzyl alcohol, cetyl alcohol, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, toluamine, white petrolatum
Butenafine Hydrochloride Cream 1%
Contains the Drug: BUTENAFINE HYDROCHLORIDE
Antifungal
Clinically Proven to Cure Most Jock Itch

(b) (4)

NDC 51672-2101-1

Compare to the active ingredient in Lotrimin Ultra® Jock Itch*

Clinically Proven to Cure Most Jock Itch

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Chafing*

Butenafine Hydrochloride Cream 1%

Antifungal

Clinically Proven to Cure Most Jock Itch

Butenafine Hydrochloride Cream 1%

Antifungal

NET WT 15 g (0.53 oz)

Butenafine Hydrochloride Cream 1% Antifungal

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

T174
B75.2
ENG19.53

LPK-7033-0
1016-0
M53

*All trademarks are property of their respective owners.
This product is not affiliated with the makers/owners of Lotrimin Ultra®.

Distributed by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
TARO is a registered trademark of
Taro Pharmaceuticals U.S.A., Inc.
Made in Canada.

TARO

N 3 51672 21011 3

NO VARNISH ON THIS FLAP

Drug Facts

Active ingredient	Purpose
Butenafine hydrochloride 1%.....	Antifungal

Uses

- cures most jock itch
- relieves itching, burning, cracking, and scaling which accompany this condition

Warnings

For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Drug Facts (continued)

Directions

- adults and children 12 years and older:
  - use the tip of the cap to break the seal and open the tube
  - wash the affected skin with soap and water and dry completely before applying
  - apply once a day to affected skin for 2 weeks or as directed by a doctor
  - wash hands after each use
- children under 12 years: ask a doctor

Other information

- do not use if seal on tube is broken or not visible
- store between 20° to 25° C (68° to 77° F)

Inactive ingredients

benzyl alcohol, cetyl alcohol, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, toluamine, white petrolatum

Questions? Call 1-866-923-4914

Butenafine Hydrochloride Cream 1%

Antifungal

Clinically Proven to Cure Most Jock Itch

Contains the Drug BUTENAFINE HYDROCHLORIDE

(b) (4)

NDC 51672-2101-9

Compare to the active ingredient in Lotrimin Ultra® Jock Itch*

Clinically Proven to Cure Most Jock Itch

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Chafing*

Butenafine Hydrochloride Cream 1%

Antifungal

LPK-7035-0
1016-0
322

T175
B76.2
ENG19.54

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

Clinically Proven to Cure Most Jock Itch

Butenafine Hydrochloride Cream 1%

Antifungal

NET WT 24 g (0.85 oz)

Butenafine Hydrochloride Cream 1% Antifungal

*All trademarks are property of their respective owners. This product is not affiliated with the makers/owners of Lotrimin Ultra®.

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

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

N 3 51672 21019 9

NO VARNISH ON THIS FLAP

Drug Facts

Active ingredient — **Purpose**
Butenafine hydrochloride 1% ..... Antifungal

Uses
- cures most jock itch
- relieves itching, burning, cracking, and scaling which accompany this condition

Warnings
For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Questions? Call 1-866-923-4914

Drug Facts (continued)

Directions
- adults and children 12 years and older:
  - use the tip of the cap to break the seal and open the tube
  - wash the affected skin with soap and water and dry completely before applying
  - apply once a day to affected skin for 2 weeks or as directed by a doctor
  - wash hands after each use
- children under 12 years: ask a doctor

Other information
- do not use if seal on tube is broken or not visible
- store between 20° to 25° C (68° to 77° F)

Inactive ingredients
benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, trolamine, white petrolatum

Butenafine Hydrochloride Cream 1% Antifungal

Contains the Drug: BUTENAFINE HYDROCHLORIDE

Clinically Proven to Cure Most Jock Itch

(b) (4)

NDC 51672-2101-2

Compare to the active ingredient in Lotrimin Ultra® Jock Itch*

Clinically Proven to Cure Most Jock Itch

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Chafing*

Butenafine Hydrochloride Cream 1%

Antifungal

NET WT 30 g (1 oz)

LPK-7037-1
1016-1
181

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

T175
B76.2
ENG19.54

NO VARNISH ON THIS FLAP

Clinically Proven to Cure Most Jock Itch

Butenafine Hydrochloride Cream 1% Antifungal

*All trademarks are property of their respective owners. This product is not affiliated with the makers/owners of Lotrimin Ultra®.

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

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

N 3 51672 21012 0

Drug Facts

Active ingredient — **Purpose**
Butenafine hydrochloride 1% ..... Antifungal

Uses
- cures most jock itch
- relieves itching, burning, cracking, and scaling which accompany this condition

Warnings
For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Contrd Center right away.

Drug Facts (continued)

Directions
- adults and children 12 years and older:
- use the tip of the cap to break the seal and open the tube
- wash the affected skin with soap and water and dry completely before applying
- apply once a day to affected skin for 2 weeks or as directed by a doctor
- wash hands after each use
- children under 12 years: ask a doctor

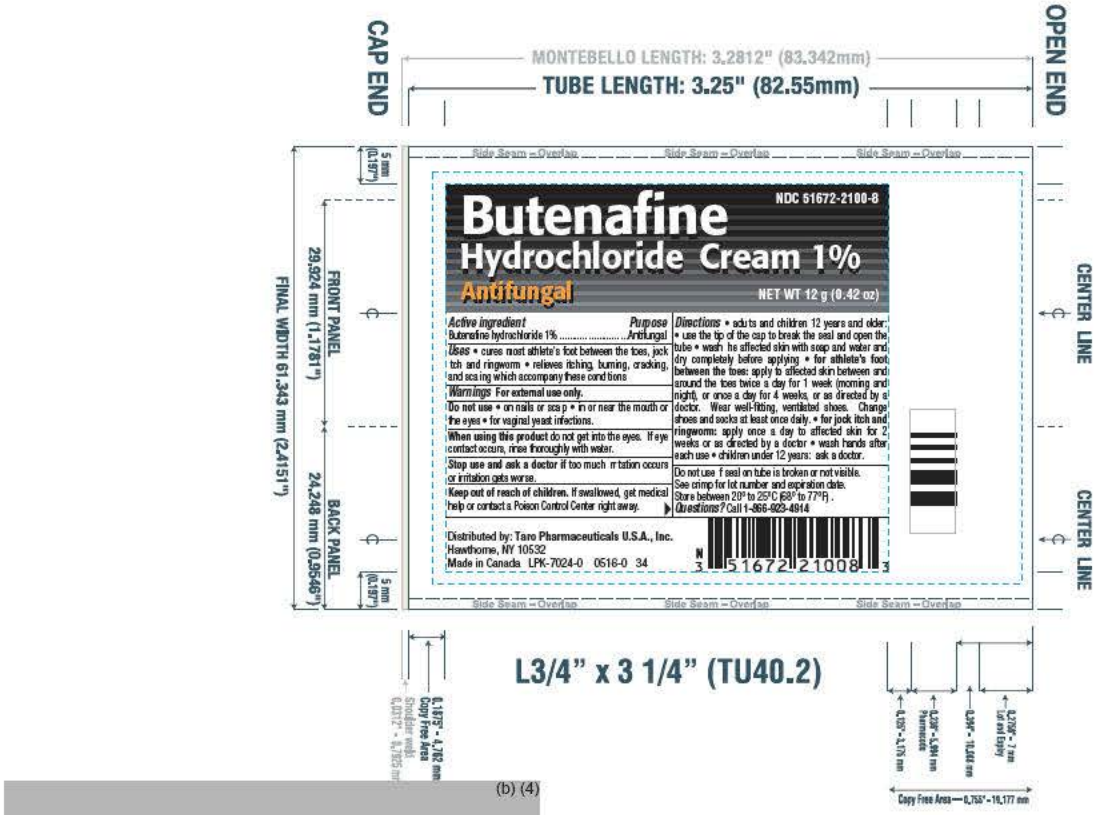
Other information
- do not use if seal on tube is broken or not visible
- store between 20° to 25° C (68° to 77° F)

Inactive ingredients
benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol diacprylate, purified water, sodium benzoate, stearic acid, tolamine, white petrolatum

Questions? Call 1-866-923-4914

Butenafine Hydrochloride Cream 1% — Contains the Drug: BUTENAFINE HYDROCHLORIDE — Antifungal — Clinically Proven to Cure Most Jock Itch

(b) (4)


CAP END
OPEN END
MONTEBELLO LENGTH: 3.2812" (83.342mm)
TUBE LENGTH: 3.25" (82.55mm)
FINAL WIDTH 61.343 mm (2.4151")
FRONT PANEL
29.924 mm (1.1781")
BACK PANEL
24.248 mm (0.9546")
5 mm (0.197")
5 mm (0.197")
Side Seam – Overlap
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Side Seam – Overlap
Side Seam – Overlap
Side Seam – Overlap
CENTER LINE
CENTER LINE
Butenafine
Hydrochloride Cream 1%
Antifungal
NDC 51672-2100-8
NET WT 12 g (0.42 oz)
Active ingredient
Butenafine hydrochloride 1% .....
Purpose
Antifungal
Uses • cures most athlete's foot between the toes, jock itch and ringworm • relieves itching, burning, cracking, and scaling which accompany these conditions
Warnings For external use only.
Do not use • on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections.
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions • adults and children 12 years and older: • use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. • for jock itch and ringworm: apply once a day to affected skin for 2 weeks or as directed by a doctor • wash hands after each use • children under 12 years: ask a doctor.
Do not use if seal on tube is broken or not visible.
See crimp for lot number and expiration date.
Store between 20° to 25°C (68° to 77°F).
Questions? Call 1-866-923-4914
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
Made in Canada LPK-7024-0 0516-0 34
N 3 51672 21008 3
L3/4" x 3 1/4" (TU40.2)
0.153" - 4.782 mm
Copy Free Area
Shoulder radii
0.0312" - 0.7925 mm
0.139" - 3.176 mm
0.238" - 5.994 mm
0.344" - 10.004 mm
0.278" - 7 mm
Lot and Expiry
Copy Free Area — 0.753" - 19.177 mm

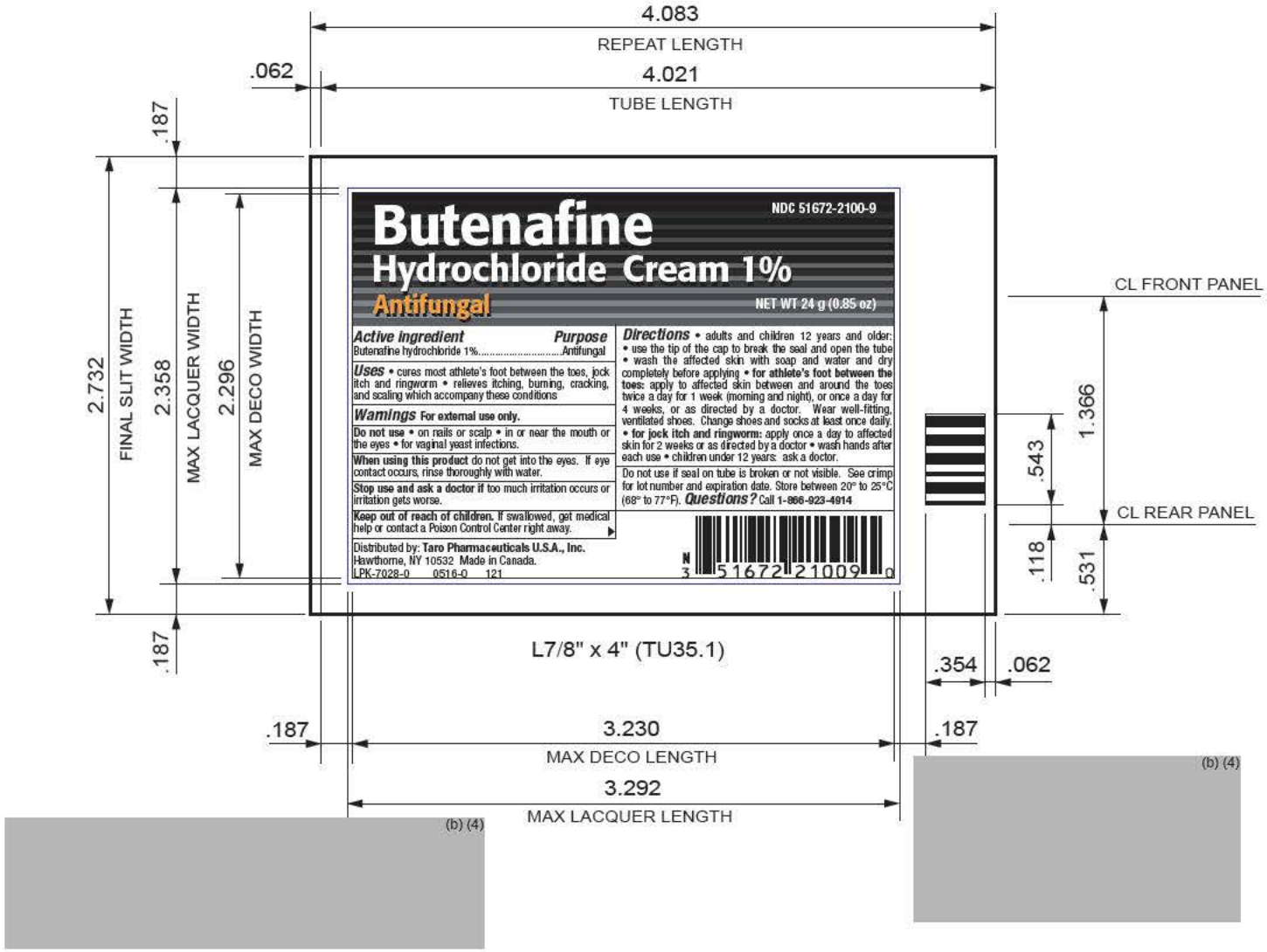
(b) (4)

(b) (4)

TU43.2 - 3/4" x 4 1/4"

(b) (4)

(b) (4)


4.083
REPEAT LENGTH
.062
4.021
TUBE LENGTH
.187
2.732
FINAL SLIT WIDTH
2.358
MAX LACQUER WIDTH
2.296
MAX DECO WIDTH
Butenafine
Hydrochloride Cream 1%
Antifungal
NDC 51672-2100-9
NET WT 24 g (0.85 oz)
Active ingredient
Purpose
Butenafine hydrochloride 1%.....Antifungal
Uses • cures most athlete's foot between the toes, jock itch and ringworm • relieves itching, burning, cracking, and scaling which accompany these conditions
Warnings For external use only.
Do not use • on nails or scalp • in or near the mouth or the eyes • for vaginal yeast infections.
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 Made in Canada.
LPK-7028-0 0516-0 121
Directions • adults and children 12 years and older: • use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. • for jock itch and ringworm: apply once a day to affected skin for 2 weeks or as directed by a doctor • wash hands after each use • children under 12 years: ask a doctor.
Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date. Store between 20° to 25°C (68° to 77°F). Questions? Call 1-866-923-4914
3 51672 21009 0
CL FRONT PANEL
1.366
.543
CL REAR PANEL
.118
.531
.187
L7/8" x 4" (TU35.1)
.354
.062
.187
3.230
MAX DECO LENGTH
.187
3.292
MAX LACQUER LENGTH
(b) (4)
(b) (4)
(b) (4)

TU13.3 - 1" x 4"

(b) (4)

(b) (4)

NDC 51672-2100-8

Compare to the active ingredient in Lotrimin Ultra®*

Clinically Proven to Cure Most Athlete's Foot between the Toes

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Cracking*

1 Week Treatment Option For Athlete's Foot See Directions

Butenafine Hydrochloride Cream 1%

Antifungal

T174
B75.2
ENG19.53

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

Clinically Proven to Cure Most Athlete's Foot between the Toes

Butenafine Hydrochloride Cream 1%

Antifungal

NET WT 12 g (0 42 oz)

Butenafine Hydrochloride Cream 1% Antifungal

LPK-7023-1
1016-1
55

*All trademarks are property of their respective owners.
This product is not affiliated with the makers/owners of Lotrimin Ultra®.

Distributed by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
TARO is a registered trademark of
Taro Pharmaceuticals U.S.A., Inc.
Made in Canada

NO VARNISH ON THIS FLAP

Drug Facts

Active ingredient	Purpose
Butenafine hydrochloride 1%	Antifungal

Uses

- cures most athlete's foot between the toes
- Effectiveness on the bottom or sides of foot is unknown.
- cures most jock itch and ringworm
- relieves itching, burning, cracking, and scaling which accompany these conditions

Warnings

For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and older:
- use the tip of the cap to break the seal and open the tube
- wash the affected skin with soap and water and dry completely before applying
- for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
- for jock itch and ringworm: apply once a day to affected skin for 2 weeks or as directed by a doctor.
- wash hands after each use
- children under 12 years: ask a doctor

Other information

- do not use if seal on tube is broken or not visible
- store between 20° to 25° C (68° to 77° F)

Inactive ingredients

benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, tolamine, white petrolatum

Questions? Call 1-866-923-4914

Butenafine Hydrochloride Cream 1% Antifungal

Contains the Drug: BUTENAFINE HYDROCHLORIDE

Clinically Proven to Cure Most Athlete's Foot between the Toes

ATTACHED LEGEND TO ALL DIGITAL MECHANICALS

STANDARD FORMAT:
Helvetica Neue 90% Horizontal Scale
Variable horizontal scale adheres to 39 characters per inch

Drug Facts - 14 pt helvetica Neue Bold Italic

Headings - 8 pt helvetica Neue Bold Italic

Sub Heads - 6 pt helvetica Neue Bold

Text - 6 pt helvetica Neue Roman

Border - 1 pt rule, 3/64" gap all around

Barline - 2.5 pt Rule

Hairline - .5 pt Rule

Certified by:
MS

NDC 51672-2100-1

Compare to the active ingredient in Lotrimin Ultra®*

Clinically Proven to Cure Most Athlete's Foot between the Toes

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Cracking*

1 Week Treatment Option For Athlete's Foot See Directions

Butenafine Hydrochloride Cream 1%

Antifungal

T174
B75.2
ENG19.53

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

Clinically Proven to Cure Most Athlete's Foot between the Toes

Butenafine Hydrochloride Cream 1%

Antifungal

NET WT 15 g (0 53 oz)

Butenafine Hydrochloride Cream 1% Antifungal

LPK-7025-0
1016-0
M51

*All trademarks are property of their respective owners.
This product is not affiliated with the makers/owners of Lotrimin Ultra®.

Distributed by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
TARO is a registered trademark of
Taro Pharmaceuticals U.S.A., Inc.
Made in Canada

NO VARNISH ON THIS FLAP

Drug Facts

Active ingredient	Purpose
Butenafine Hydrochloride 1%	Antifungal

Uses

- cures most athlete's foot between the toes
- Effectiveness on the bottom or sides of foot is unknown.
- cures most jock itch and ringworm
- relieves itching, burning, cracking, and scaling which accompany these conditions

Warnings

For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Drug Facts (continued)

Directions

- adults and children 12 years and older:
- use the tip of the cap to break the seal and open the tube
- wash the affected skin with soap and water and dry completely before applying
- for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
- for jock itch and ringworm: apply once a day to affected skin for 2 weeks or as directed by a doctor.
- wash hands after each use
- children under 12 years: ask a doctor

Other information

- do not use if seal on tube is broken or not visible
- store between 20° to 25° C (68° to 77° F)

Inactive ingredients

benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, tolamine, white petrolatum

Questions? Call 1-866-923-4914

Butenafine Hydrochloride Cream 1%
Antifungal
Clinically Proven to Cure Most Athlete's Foot Between the Toes
Contains the Drug BUTENAFINE HYDROCHLORIDE

(b) (4)

NDC 51672-2100-9

Compare to the active ingredient in Lotrimin Ultra®*

Clinically Proven to Cure Most Athlete's Foot between the Toes

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Cracking*

1 Week
Treatment Option
For Athlete's Foot
See Directions

Butenafine
Hydrochloride Cream 1%
Antifungal

LPK-7027-0
10160-0
321

T175
B76.2
ENG19.54

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

Clinically Proven to Cure Most Athlete's Foot between the Toes

Butenafine
Hydrochloride Cream 1%
Antifungal

NET WT 24 g (0.85 oz)

Butenafine
Hydrochloride
Cream 1%
Antifungal

N 3 51672 21009 0

* All trademarks are property of their respective owners. This product is not affiliated with the makers/owners of Lotrimin Ultra®.

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

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

NO VARNISH
ON THIS FLAP

Drug Facts

Active ingredient — **Purpose**
Butenafine hydrochloride 1% ..... Antifungal

Uses
- cures most athlete's foot between the toes.
Effectiveness on the bottom or sides of foot is unknown.
- cures most jock itch and ringworm
- relieves itching, burning, cracking, and scaling which accompany these conditions

Warnings
For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Drug Facts (continued)

Directions
- adults and children 12 years and older:
- use the tip of the cap to break the seal and open the tube
- wash the affected skin with soap and water and dry completely before applying
- for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
- for jock itch and ringworm: apply between and around the toes apply once a day to affected skin for 2 weeks or as directed by a doctor.
- wash hands after each use — 1 week twice a day or 4 weeks once a day
- children under 12 years: ask a doctor

Other information
- store between 20° to 25° C (68° to 77° F)
- do not use if seal on tube is broken or not visible

Inactive ingredients benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol diacrylate, purified water, sodium benzoate, stearic acid, triethanolamine, white petrolatum

Questions? Call 1-866-923-4914

Butenafine Hydrochloride Cream 1%
Contains the Drug: BUTENAFINE HYDROCHLORIDE
Antifungal
Clinically Proven to Cure Most Athlete's Foot between the Toes

(b) (4)

NDC 51672-2100-2

Compare to the active ingredient in Lotrimin Ultra®*

Clinically Proven to Cure Most Athlete's Foot between the Toes

Contains the Drug: BUTENAFINE HYDROCHLORIDE

- *Prescription Strength*
- *Relieves Itching, Burning and Cracking*

1 Week Treatment Option For Athlete's Foot See Directions

Butenafine Hydrochloride Cream 1%

Antifungal

LPK-7029-1
1016-1
16

T175
B76.2
ENG19.54

NO VARNISH/ NO AQ
NO COPY / NO COLOR
THIS FLAP FOR LOT #
AND EXP DATE PRINT

Clinically Proven to Cure Most Athlete's Foot between the Toes

Butenafine Hydrochloride Cream 1%

Antifungal

NET WT 30 g (1 oz)

Butenafine Hydrochloride Cream 1% Antifungal

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

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

N 3 51672 21002 1

TARO

NO VARNISH ON THIS FLAP

Drug Facts

Active ingredient	Purpose
Butenafine hydrochloride 1%	Antifungal

Uses

- cures most athlete's foot between the toes.
  Fed/tiredness on the bottom or sides of foot is unknown.
- cures most jock itch and ringworm
- relieves itching, burning, cracking, and scaling which accompany these conditions

Warnings

For external use only

Do not use
- on nails or scalp
- in or near the mouth or the e/es
- for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Drug Facts (continued)

Directions

- adults and children 12 years and older:
  - use the tip of the cap to break the seal and open the tube
  - wash the affected skin with soap and water and dry completely before applying
  - for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
  - for jock itch and ringworm: apply between and around the toes apply once a day to affected skin for 2 weeks or as directed by a doctor.
    1 week twice a day or 4 weeks once a day
  - wash hands after each use
- children under 12 years: ask a doctor

Other information

- do not use if seal on tube is broken or not visible
- store between 20° to 25° C (68° to 77° F)

Inactive ingredients

benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol diacrylate, purified water, sodium benzoate, stearic acid, triethanine, white petrolatum

Questions?

Call 1-866-923-4914

Butenafine Hydrochloride Cream 1% Antifungal

Contains the Drug: BUTENAFINE HYDROCHLORIDE

Clinically Proven to Cure Most Athlete's Foot between the Toes

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205818

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	1/4/2017
ANDA Number(s)	205181
Review Number	4
Applicant Name	Taro Pharmaceuticals USA, Inc.
Established Name & Strength(s)	Butenafine Hydrochloride Cream, 1%
Proposed Proprietary Name	None
Submission Received Date	11/16/2016
Labeling Reviewer	Charlie Hoppes
Labeling Team Leader	Ann Vu

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated November 16, 2016.

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. The below comments are from the labeling review C3 based on the submission dated 6/3/16.

Reviewer Comments:

LABELING
GENERAL COMMENTS

Please note that there have been recent and significant changes to the labeling of the Reference Listed Drug (RLD), NDA 021307/S-015, approved December 18, 2015. Revise your labels and labeling accordingly. Please note that you need not include the pricing information approved for the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.
However, prior to the submission of your amendment, please check labeling resources, includingDRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling 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://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Response:
The carton labeling for Athlete's foot (12 g, 15 g, 24 g and 30 g) and Jock Itch (12 g, 15 g, 24 g and 30 g) have been revised as per the changes made to Reference Listed Drug (RLD), NDA 021307/S-015, approved December 18, 2015 and is included in Module 1.14.2.1. The side-by-side comparison of the current vs. proposed labeling (Athlete's foot and Jock Itch) is provided in Module 1.14.2.1. In addition, the SPL for Athlete's Foot and Jock Itch has been revised and is included in Module 1.14.2.2.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** NDA 021307/S-015 **Supplement Approval Date:** 12/18/2015 **Proprietary Name:** Lotrimin Ultra **Established Name:** Butenafine HCl Cream **Description of Supplement:** Adds promotional information and the claim "1 week treatment option".
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):**
☐ **OTHER (Describe):**

Reviewer Assessment:

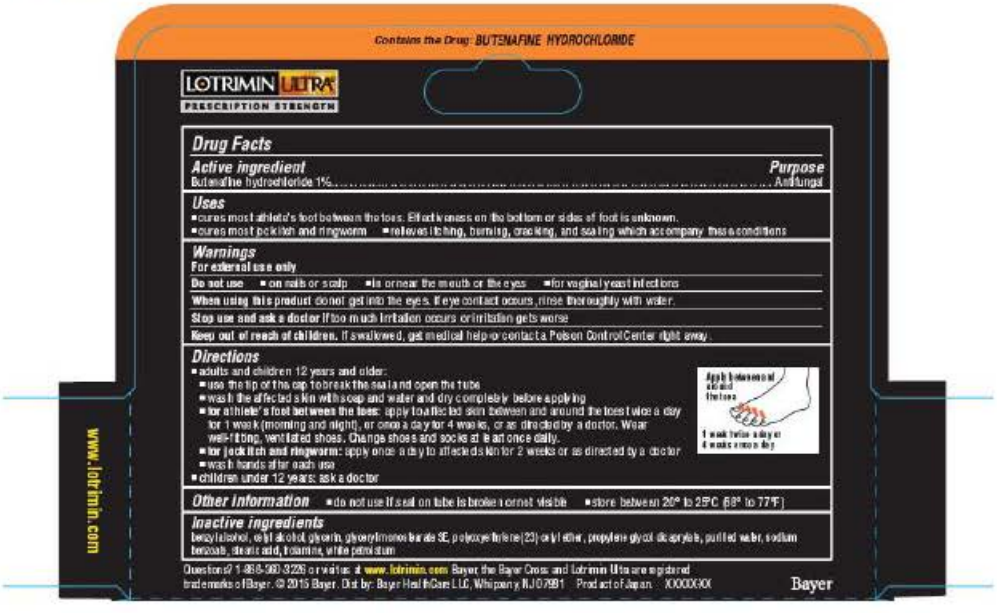
Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES** Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **NA** Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

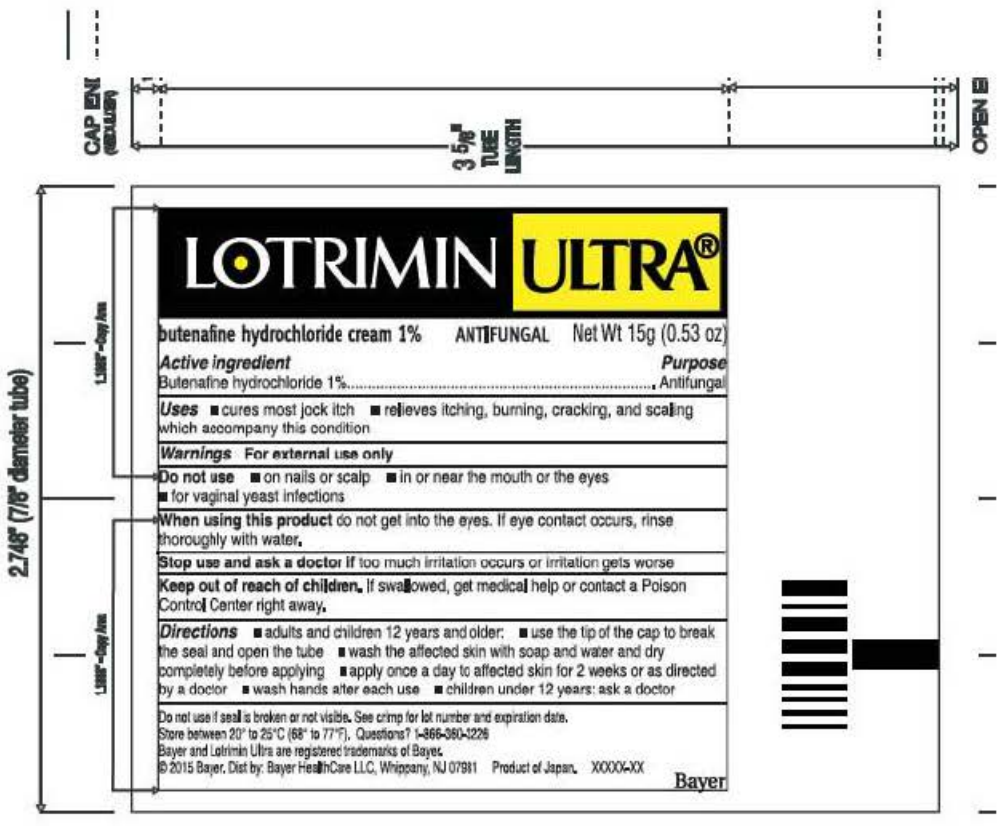
3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021307/S-015, approved 12/18/2015]

Certified by: dv
10.5.15 K MPLS




4 9/16" TUBE LENGTH
LOTRIMIN ULTRA®
butenafine hydrochloride cream 1%
ANTIFUNGAL
Net Wt 30g (1.1 oz)
Active ingredient
Purpose
Butenafine hydrochloride 1%..... Antifungal
Uses ■ cures most athlete's foot between the toes, jock itch and ringworm ■ relieves itching, burning, cracking, and scaling which accompany these conditions
Warnings For external use only
Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions
■ adults and children 12 years and older: ■ use the tip of the cap to break the seal and open the tube ■ wash the affected skin with soap and water and dry completely before applying ■ for athlete's foot between the toes: apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. ■ for jock itch and ringworm: apply once a day to affected skin for 2 weeks or as directed by a doctor ■ wash hands after each use ■ children under 12 years: ask a doctor
Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date.
Store between 20° to 25°C (68° to 77°F). Questions? 1-866-360-3226
Bayer and Lotrimin Ultra are registered trademarks of Bayer.
© 2015 Bayer. Dist by: Bayer HealthCare LLC, Whippany, NJ 07981 Product of Japan. XXXXX-XX
Bayer


3 5/8" TUBE LENGTH
2.748" (7/8" diameter tube)
LOTRIMIN ULTRA®
butenafine hydrochloride cream 1%
ANTIFUNGAL
Net Wt 15g (0.53 oz)
Active ingredient
Purpose
Butenafine hydrochloride 1%..... Antifungal
Uses ■ cures most jock itch ■ relieves itching, burning, cracking, and scaling which accompany this condition
Warnings For external use only
Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions ■ adults and children 12 years and older: ■ use the tip of the cap to break the seal and open the tube ■ wash the affected skin with soap and water and dry completely before applying ■ apply once a day to affected skin for 2 weeks or as directed by a doctor ■ wash hands after each use ■ children under 12 years: ask a doctor
Do not use if seal is broken or not visible. See crimp for lot number and expiration date.
Store between 20° to 25°C (68° to 77°F). Questions? 1-866-360-3226
Bayer and Lotrimin Ultra are registered trademarks of Bayer.
© 2015 Bayer. Dist by: Bayer HealthCare LLC, Whippany, NJ 07981 Product of Japan. XXXXX-XX
Bayer


Contains the Drug: BUTENAFINE HYDROCHLORIDE
LOTRIMIN ULTRA
PRESCRIPTION STRENGTH
BONUS
15g for the price of 12g
25% MORE
Relieves: Itching Burning Chafing
Clinically Proven to Cure Most Jock Itch
LOTRIMIN ULTRA
butenafine hydrochloride cream 1% ANTIFUNGAL
LOTRIMIN ULTRA
butenafine hydrochloride cream 1% ANTIFUNGAL NET WT 15g (0.53 OZ)
0 11017-408-27 7
Questions? 1-866-360-3226
or visit us at www.lotrimin.com
PRESCRIPTION STRENGTH
LOTRIMIN ULTRA
Contains the Drug: BUTENAFINE HYDROCHLORIDE
LOTRIMIN ULTRA
PRESCRIPTION STRENGTH
Drug Facts
Active Ingredient
Butenafine hydrochloride 1%
Purpose
Antifungal
Uses
cures most jock itch
relieves itching, burning, cracking, and scaling which accompany this condition
Warnings
For external use only
Do not use on nails or scalp in or near the mouth or the eyes for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse eyes thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions
adults and children 12 years and over:
use the flip off the cap to break the seal and open the tube
wash the affected skin with soap and water and dry completely before applying
apply once a day to affected skin for 2 weeks or as directed by a doctor
wash hands after each use
children under 12 years: ask a doctor
Other information
do not use if seal on tube is broken or not visible
store between 20° to 25°C (68° to 77°F)
Inactive ingredients
benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, trolamine, white petrolatum
Questions? 1-866-360-3226 or visit us at www.lotrimin.com
Bayer
www.lotrimin.com
LOTRIMIN ULTRA
PRESCRIPTION STRENGTH
Questions? 1-866-360-3226
or visit us at www.lotrimin.com
0 11017-408-27 7

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	1/4/2017	No	N/A	N/A
PF	1/4/2017	No	N/A	N/A

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/4/2017.

Table 3 provides Orange Book patents for the Model Labeling NDA 021307 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Inactive ingredients benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, trolamine, white petrolatum	***Inactive ingredients*** benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, trolamine, white petrolatum	**No Changes**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Distributed by: **Taro Pharmaceuticals U.S.A., Inc.** Hawthorne, NY 10532 TARO is a registered trademark of Taro Pharmaceuticals U.S.A., Inc. Made in Canada.	Distributed by: **Taro Pharmaceuticals U.S.A., Inc.** Hawthorne, NY 10532 TARO is a registered trademark of Taro Pharmaceuticals U.S.A., Inc. Made in Canada	**No Changes**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	AF & JI: 12 g, 15 g, 24 g, 30 g	6/3/2016	Satisfactory
Carton	Final	1's all sizes	11/16/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
SPL Data Elements		10/2016	11/16/2016	Satisfactory

Thuyanh Vu

Digitally signed by Thuyanh Vu
Date: 1/04/2017 12:59:36PM
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LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	7/29/2016
ANDA Number(s)	205181
Review Number	3
Applicant Name	Taro Pharmaceuticals Inc.
Established Name & Strength(s)	Butenafine Hydrochloride Cream, 1%
Proposed Proprietary Name	None
Submission Received Date	6/3/2016
Labeling Reviewer	Charlie Hoppes
Labeling Team Leader	John Grace

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on July 29, 2016, based on your submission dated June 3, 2016.

GENERAL COMMENTS
Please note that there have been recent and significant changes to the labeling of the Reference Listed Drug (RLD), NDA 021307/S-015, approved December 18, 2015. Revise your labels and labeling accordingly. Please note that you need not include the pricing information approved for the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling 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://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. The below comments are from the labeling review C2 based on the submission dated 2/4/13.

Reviewer Comments:

LABELING

Comment 1
CONTAINERS FOR ATHLETE'S FOOT (12 g, 15 g, 24 g, 30 g tubes)

a. Delete "Athlete's Foot Cream", as it does not appear in the reference listed drug's (RLD) labels.

Response 1a
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

b. Make the established drug name "Butenafine Hydrochloride Cream 1%" the most prominent feature, excluding reference under the "Drug Facts".

Response 1b
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

c. Add a bar line between the "Directions" section and "Do not use if seal on tube..." We refer you to the RLD labels for guidance as well as 21 CFR 201.66 (d) (8) for formatting.

Response 1c
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

d. Add "Questions? Call 1-866-923-4914". We refer you to the RLD labels for guidance.

Response 1d
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

e. Delete [redacted] (b) (4) *as it does not appear in the RLD labels. We refer you to the RLD labels for guidance.*

Response 1e
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

f. There are missing hairlines within the "Warnings" section. We refer you to 21 CFR 201.66(d) (8) for format information. We also refer you to the RLD labels for Guidance.

Response 1f
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

Comment 2
CARTONS FOR ATHLETE'S FOOT (12 g, 15 g, 24 g, 30 g tubes)

a. Delete "Athlete's Foot Cream" on all panels as it does not appear in the reference listed drug's (RLD) labeling.

Response 2a
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

b. Refer to the comment "b" under "CONTAINERS FOR ATHLETE'S FOOT."

Response 2b
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

c. Delete (b) (4) *as they do not appear in the RLD's labeling.*

Response 2c
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

Comment 3
CONTAINERS FOR JOCK ITCH (12 g, 15 g, 24 g, 30 g tubes)

a. Delete (b) (4) *as it does not appear in the RLD's labels.*

Response 3a
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

b. Refer to the comments "b, c, d, and f" under "CONTAINERS FOR ATHLETE'S FOOT.

Response 3b
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

c. Delete (b) (4) *as it does not appear in the RLD's labels. We refer you to the RLD labels for guidance.*

Response 3c
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

Comment 4
CARTONS FOR JOCK ITCH (12 g, 15 g, 24 g, 30 g tubes)

a. *Delete* (b) (4) *on all panels as it does not appear in the reference listed drug's (RLD) labeling.*

Response 4a
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

b. *Refer to the comment "b" under "CONTAINERS FOR ATHLETE'S FOOT."*

Response 4b
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

c. *Delete* (b) (4) *as it does not appear in the RLD's labeling.*

Response 4c
The labeling has been revised per the Agency's request and is included in Module 1.14.2.1.

Comment 5
SPL DATA ELEMENTS FOR JOCK ITCH
Inactive Ingredients: Add "ceteth-23".

Submit your revised labeling electronically in final print format. Furthermore, submit a legend that states the font sizes for the headings, subheadings, etc. for each container and carton label.

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

Response 5
The SPL Data Elements for Jock Itch has been revised per the Agency's request and is included in Module 1.14.2.2.

In addition, a side-by-side comparison of the current vs. proposed labeling (Athlete's foot and Jock Itch) is provided in Module 1.14.2.1.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 021307/S-015 **Supplement Approval Date:** 12/18/2015 **Proprietary Name:** Lotrimin Ultra **Established Name:** Butenafine hydrochloride cream **Description of Supplement:** Adds promotional information and the claim "1 week treatment option".
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):**
☐ **OTHER (Describe):**

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO** Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **NA** Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

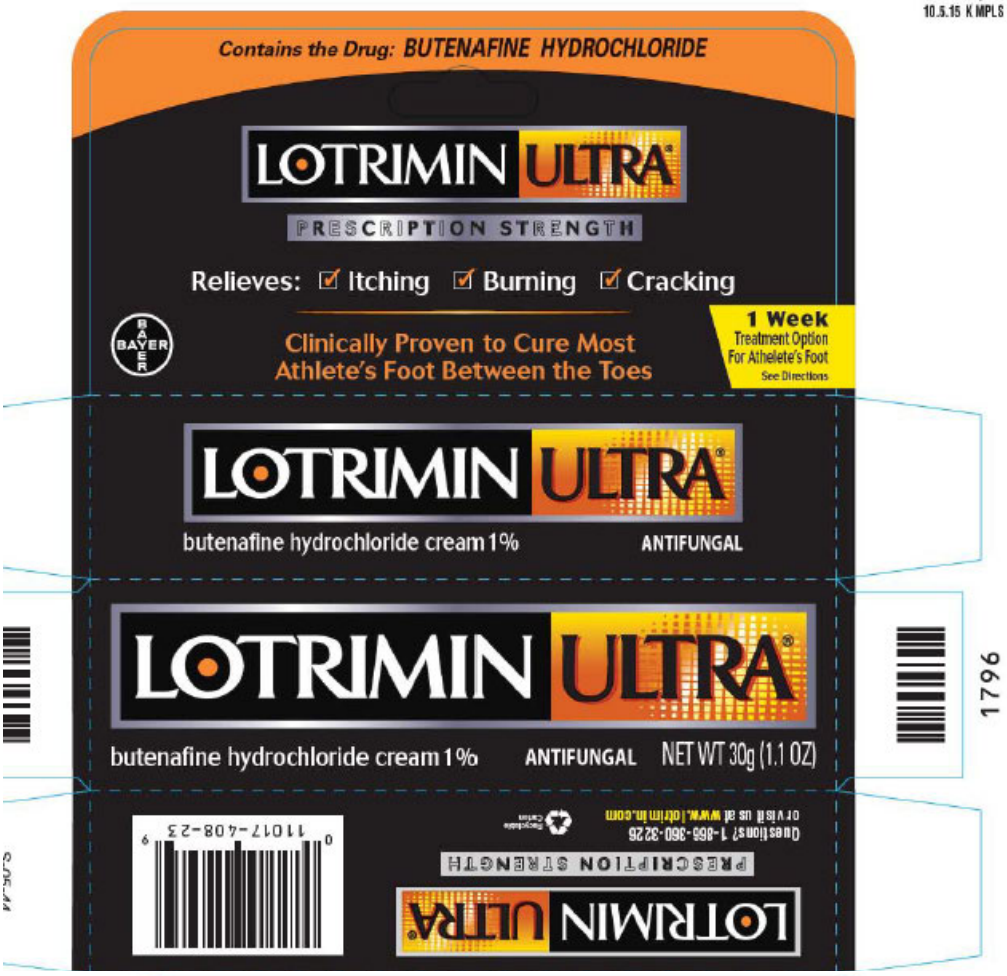
Reviewer Comments:

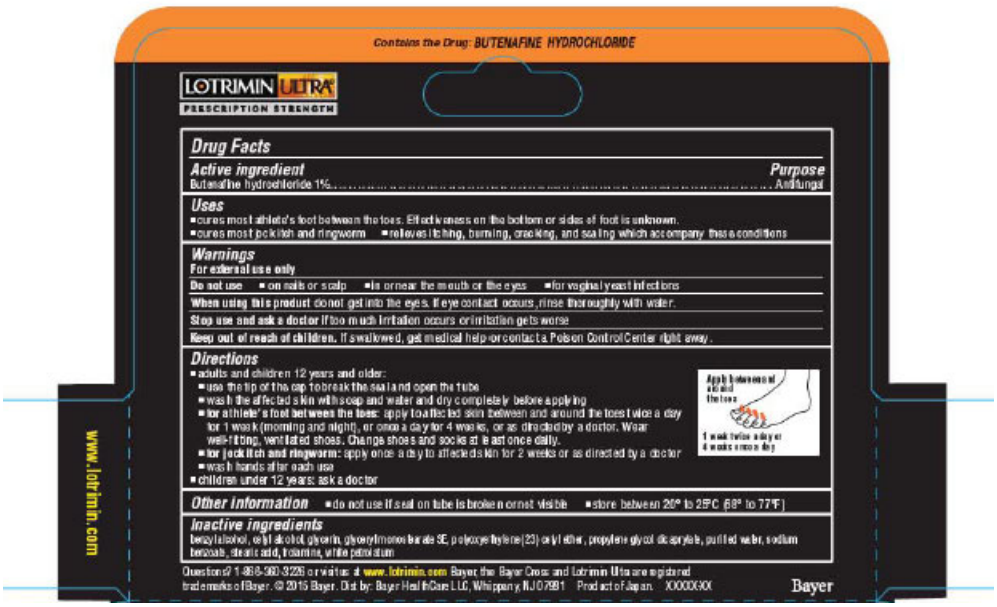
Sponsor will be requested to update to the last approved labeling of the RLD.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021307/S-015, approved 12/18/2015]

Certified by: dv
10.5.15 K MPLS





4 9/16" TUBE LENGTH

LOTRIMIN ULTRA®

butenafine hydrochloride cream 1% ANTIFUNGAL Net Wt 30g (1.1 oz)

Active ingredient ***Purpose***

Butenafine hydrochloride 1%....................Antifungal

Uses ■ cures most athlete's foot between the toes, jock itch and ringworm ■ relieves itching, burning, cracking, and scaling which accompany these conditions

Warnings For external use only

Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

■ adults and children 12 years and older: ■ use the tip of the cap to break the seal and open the tube ■ wash the affected skin with soap and water and dry completely before applying ■ **for athlete's foot between the toes:** apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. ■ **for jock itch and ringworm:** apply once a day to affected skin for 2 weeks or as directed by a doctor ■ wash hands after each use ■ children under 12 years: ask a doctor

Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date.
Store between 20° to 25°C (68° to 77°F). Questions? 1-866-360-3226
Bayer and Lotrimin Ultra are registered trademarks of Bayer.
© 2015 Bayer. Dist by: Bayer HealthCare LLC, Whippany, NJ 07981 Product of Japan. XXXXX-XX
Bayer

CAP END (SEALER) 3 5/8" TUBE LENGTH OPEN END

2.748" (7/8" diameter tube)

LOTRIMIN ULTRA®

butenafine hydrochloride cream 1% ANTIFUNGAL Net Wt 15g (0.53 oz)

Active ingredient ***Purpose***

Butenafine hydrochloride 1%....................Antifungal

Uses ■ cures most jock itch ■ relieves itching, burning, cracking, and scaling which accompany this condition

Warnings For external use only

Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions ■ adults and children 12 years and older: ■ use the tip of the cap to break the seal and open the tube ■ wash the affected skin with soap and water and dry completely before applying ■ apply once a day to affected skin for 2 weeks or as directed by a doctor ■ wash hands after each use ■ children under 12 years: ask a doctor

Do not use if seal is broken or not visible. See crimp for lot number and expiration date.
Store between 20° to 25°C (68° to 77°F). Questions? 1-866-360-3226
Bayer and Lotrimin Ultra are registered trademarks of Bayer.
© 2015 Bayer. Dist by: Bayer HealthCare LLC, Whippany, NJ 07981 Product of Japan. XXXXX-XX
Bayer


Contains the Drug: BUTENAFINE HYDROCHLORIDE
LOTRIMIN ULTRA
PRESCRIPTION STRENGTH
BONUS
15g for the price of 12g
25% MORE
Relieves: Itching Burning Chafing
Clinically Proven to Cure Most Jock Itch
LOTRIMIN ULTRA
butenafine hydrochloride cream 1%
ANTIFUNGAL
LOTRIMIN ULTRA
butenafine hydrochloride cream 1% ANTIFUNGAL NET WT 15g (0.53 OZ)
0 11017-408-27
Questions? 1-866-360-3226
or visit us at www.lotrimin.com
PRESCRIPTION STRENGTH
LOTRIMIN ULTRA
Contains the Drug: BUTENAFINE HYDROCHLORIDE
LOTRIMIN ULTRA
PRESCRIPTION STRENGTH
Drug Facts
Active ingredient
Butenafine hydrochloride 1%
Purpose
Antifungal
Uses
cures most jock itch
relieves itching, burning, cracking, and scaling which accompany this condition
Warnings
For external use only
Do not use on nails or scalp in or near the mouth or the eyes for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse eyes thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions
adults and children 12 years and over:
use the flip off the cap to break the seal and open the tube
wash the affected skin with soap and water and dry completely before applying
apply once a day to affected skin for 2 weeks or as directed by a doctor
wash hands after each use
children under 12 years: ask a doctor
Other information
do not use if seal on tube is broken or not visible
store between 20° to 25°C (68° to 77°F)
Inactive ingredients
benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, triethanolamine, white petrolatum
Questions? 1-866-360-3226 or visit us at www.lotrimin.com
Bayer, the Bayer Cross and Lotrimin Ultra are registered trademarks of Bayer.
© 2010 Bayer, Dist by: Bayer HealthCare LLC, Whippany, NJ 07981 Product of Japan, XXXXX-XX
Bayer
www.lotrimin.com
LOTRIMIN ULTRA
PRESCRIPTION STRENGTH
Questions? 1-866-360-3226
or visit us at www.lotrimin.com
0 11017-408-27 7

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	7/29/2016	No	N/A	N/A
PF	7/29/2016	No	N/A	N/A

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/29/2016.

Table 3 provides Orange Book patents for the Model Labeling 021307 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Inactive ingredients benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, trolamine, white petrolatum	***Inactive ingredients*** benzyl alcohol, cetyl alcohol, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, trolamine, white petrolatum	**No Changes**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
		No Changes

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Distributed by: **Taro Pharmaceuticals U.S.A., Inc.** Hawthorne, NY 10532 TARO is a registered trademark of Taro Pharmaceuticals U.S.A., Inc. Made in Canada.	Distributed by: **Taro Pharmaceuticals U.S.A., Inc.** Hawthorne, NY 10532 TARO is a registered trademark of Taro Pharmaceuticals U.S.A., Inc. Made in Canada.	**No Changes**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	12 g, 15 g, 24 g, and 30 g (each indication)	6/3/2016	Revise
Carton	Final	1's	6/3/2016	Revise
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
SPL Data Elements		5/2016	6/3/2016	Revise

Charles Hoppes

Digitally signed by Charles Hoppes
Date: 8/01/2016 07:05:27AM
GUID: 508da70600028b0abae4848ffc506ecc

John Grace

Digitally signed by John Grace
Date: 8/01/2016 07:07:17AM
GUID: 508da70800028bf026504977722c3599

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (#1 Cycle)

ANDA Number:	205181
Date of Submission:	February 4, 2013
Applicant:	Taro Pharmaceuticals U.S.A., Inc.
Established Name and Strength:	Butenafine Hydrochloride Cream, 1%
Proprietary Name:	None

Labeling Comments below are considered:

☒ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on March 17, 2014, based on your submission dated February 4, 2013:

1. **CONTAINERS FOR ATHLETE'S FOOT** (12 g, 15 g, 24 g, 30 g tubes)
   a. Delete "[redacted (b) (4)] as it does not appear in the reference listed drug's (RLD) labels.
   b. Make the established drug name "Butenafine Hydrochloride Cream 1%" the most prominent feature, excluding reference under the "Drug Facts".
   c. Add a barline between the "Directions" section and "Do not use if seal on tube…" We refer you to the RLD labels for guidance as well as 21 CFR 201.66 (d) (8) for format information.
   d. Add "Questions? Call 1-866-923-4914". We refer you to the RLD labels for guidance.
   e. Delete [redacted (b) (4)] as it does not appear in the RLD labels. We refer you to the RLD labels for guidance.
   f. There are missing hairlines within the "Warnings" section. We refer you to 21 CFR 201.66(d) (8) for format information. We also refer you to the RLD labels for Guidance.
2. **CARTONS FOR ATHLETE'S FOOT** (12 g, 15 g, 24 g, 30 g tubes)
   a. Delete [redacted (b) (4)] on all panels as it does not appear in the reference listed drug's (RLD) labeling.
   b. Refer to the comment "b" under "CONTAINERS FOR ATHLETE'S FOOT."
   c. Delete the images of a foot (outside of the "Drug Facts") as they do not appear in the RLD's labeling.
3. **CONTAINERS FOR JOCK ITCH** (12 g, 15 g, 24 g, 30 g tubes)

a. Delete [redacted] (b) (4) as it does not appear in the RLD's labels.

b. Refer to the comments "b, c, d, and f" under "CONTAINERS FOR ATHLETE'S FOOT."

c. Delete [redacted] (b) (4) as it does not appear in the RLD's labels. We refer you to the RLD labels for guidance.

4. **CARTONS FOR JOCK ITCH** (12 g, 15 g, 24 g, 30 g tubes)

a. Delete [redacted] (b) (4) on all panels as it does not appear in the reference listed drug's (RLD) labeling.

b. Refer to the comment "b" under "CONTAINERS FOR ATHLETE'S FOOT."

c. Delete the [redacted] (b) (4) as it does not appear in the RLD's labeling.

5. **SPL DATA ELEMENTS FOR JOCK ITCH**

Inactive Ingredients: Add "ceteth-23".

Submit your revised labeling electronically in final print format. Furthermore, submit a legend that states the font sizes for the headings, subheadings, etc. for each container and carton label.

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

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling 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://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER for Athlete's Foot (12 g, 15 g, 24 g, 30 g tubes)	February 4, 2013	Draft	Revise
CARTON for Athlete's Foot (12 g, 15 g, 24 g, 30 g tubes)	February 4, 2013	Draft	Revise
CONTAINER for Jock itch (12 g, 15 g, 24 g, 30 g tubes)	February 4, 2013	Draft	Revise

CARTON for Jock itch (12 g, 15 g, 24 g, 30 g tubes)	February 4, 2013	Draft	Revise
SPL DATA ELEMENTS for Jock itch	February 4, 2013	N/A	Revise

FOR THE RECORD:

1. **MODEL LABELING:** Lotrimin Ultra® (Butenafine Hydrochloride) 1% cream, NDA 021307/S-013; approved 5/2/12. It is OTC switch product. S-013 provides for the revision of the claim "Full Prescription Strength" to "Prescription Strength". It also proposes to enlarge "Prescription Strength" and reposition it under the proprietary name on the fifth panel and on the principal display panel (PDP) of the carton label for Lotrimin Ultra® Athlete's Foot and Lotrimin Ultra® Jock itch. There is no pending labeling supplement at this time.

   RLD Container/Carton (30 g presentation for Athlete's foot and 12 g presentation for Jock itch shown):

LOTRIMIN ULTRA®

butenafine hydrochloride cream 1% ANTIFUNGAL Net Wt 30g (1.1 oz)

Active ingredient ***Purpose***

Butenafine hydrochloride 1%..... Antifungal

Uses ■ cures most athlete's foot between the toes, jock itch and ringworm ■ relieves itching, burning, cracking, and scaling which accompany these conditions

Warnings **For external use only**

Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

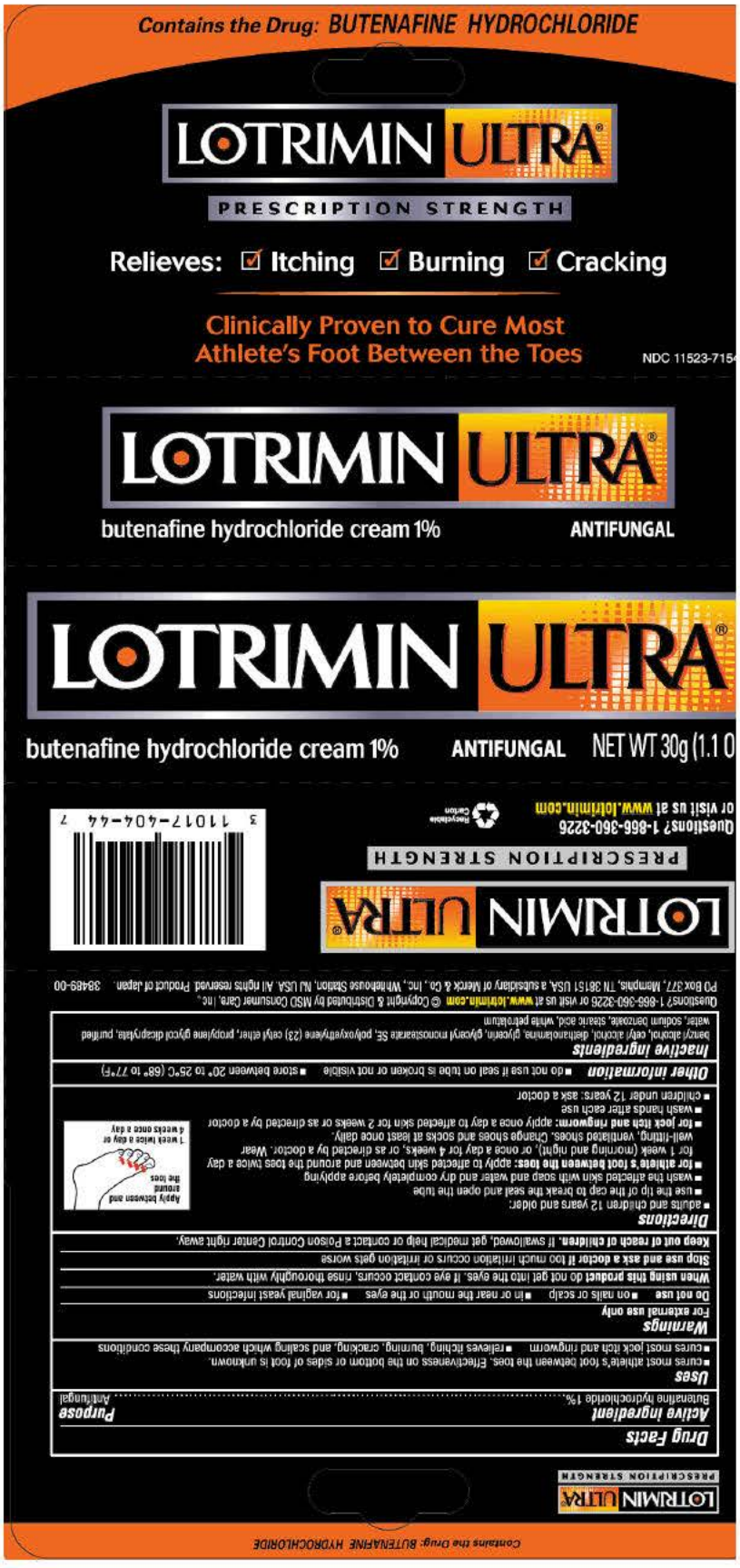
Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

■ adults and children 12 years and older: ■ use the tip of the cap to break the seal and open the tube ■ wash the affected skin with soap and water and dry completely before applying ■ **for athlete's foot between the toes:** apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. ■ **for jock itch and ringworm:** apply once a day to affected skin for 2 weeks or as directed by a doctor ■ wash hands after each use ■ children under 12 years: ask a doctor

Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date. Store between 20° to 25°C (68° to 77°F). Questions? 1-866-360-3226 Product of Japan. 27976-06


Contains the Drug: BUTENAFINE HYDROCHLORIDE
LOTRIMIN ULTRA®
PRESCRIPTION STRENGTH
Relieves: ☑ Itching ☑ Burning ☑ Cracking
Clinically Proven to Cure Most Athlete's Foot Between the Toes
NDC 11523-7154
LOTRIMIN ULTRA®
butenafine hydrochloride cream 1% ANTIFUNGAL
LOTRIMIN ULTRA®
butenafine hydrochloride cream 1% ANTIFUNGAL NET WT 30g (1.1 0
Questions? 1-866-360-3226
or visit us at www.lotrimin.com
Recyclable Carton
3 11017-4044-44 7
PRESCRIPTION STRENGTH
LOTRIMIN ULTRA®
Drug Facts
Active Ingredient
Butenafine Hydrochloride 1%
Purpose
Antifungal
Uses
■ cures most athlete's foot between the toes. Effectiveness on the bottom or sides of foot is unknown.
■ cures most jock itch and ringworm ■ relieves itching, burning, cracking, and scaling which accompany these conditions
Warnings
For external use only
Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions
■ adults and children 12 years and older:
■ use the tip of the cap to break the seal and open the tube
■ wash the affected skin with soap and water and dry completely before applying
■ for athlete's foot between the toes: apply to affected skin between and around the toes twice a day
for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor. Wear well-fitting, ventilated shoes. Change shoes and socks at least once daily.
■ for jock itch and ringworm: apply once a day to affected skin for 2 weeks or as directed by a doctor
■ wash hands after each use
■ children under 12 years: ask a doctor
Apply between and around the toes
1 week twice a day or 4 weeks once a day
Other information ■ do not use if seal on tube is broken or not visible ■ store between 20° to 25°C (68° to 77°F)
Inactive Ingredients
benzyl alcohol, cetyl alcohol, deltamonoleme, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, white petrolatum
Questions? 1-866-360-3226 or visit us at www.lotrimin.com © Copyright & Distributed by MSD Consumer Care, Inc.
PO Box 377, Memphis, TN 38151 USA, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ USA. All rights reserved. Product of Japan. 38489-00
PRESCRIPTION STRENGTH
LOTRIMIN ULTRA®
Contains the Drug: BUTENAFINE HYDROCHLORIDE

LOTRIMIN ULTRA®

butenafine hydrochloride cream 1% **ANTIFUNGAL** Net Wt 12g (0.42 oz)

Active ingredient	***Purpose***
Butenafine hydrochloride 1%	Antifungal

Uses ■ cures most jock itch
■ relieves itching, burning, cracking, and scaling which accompany this condition

Warnings **For external use only**

Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections

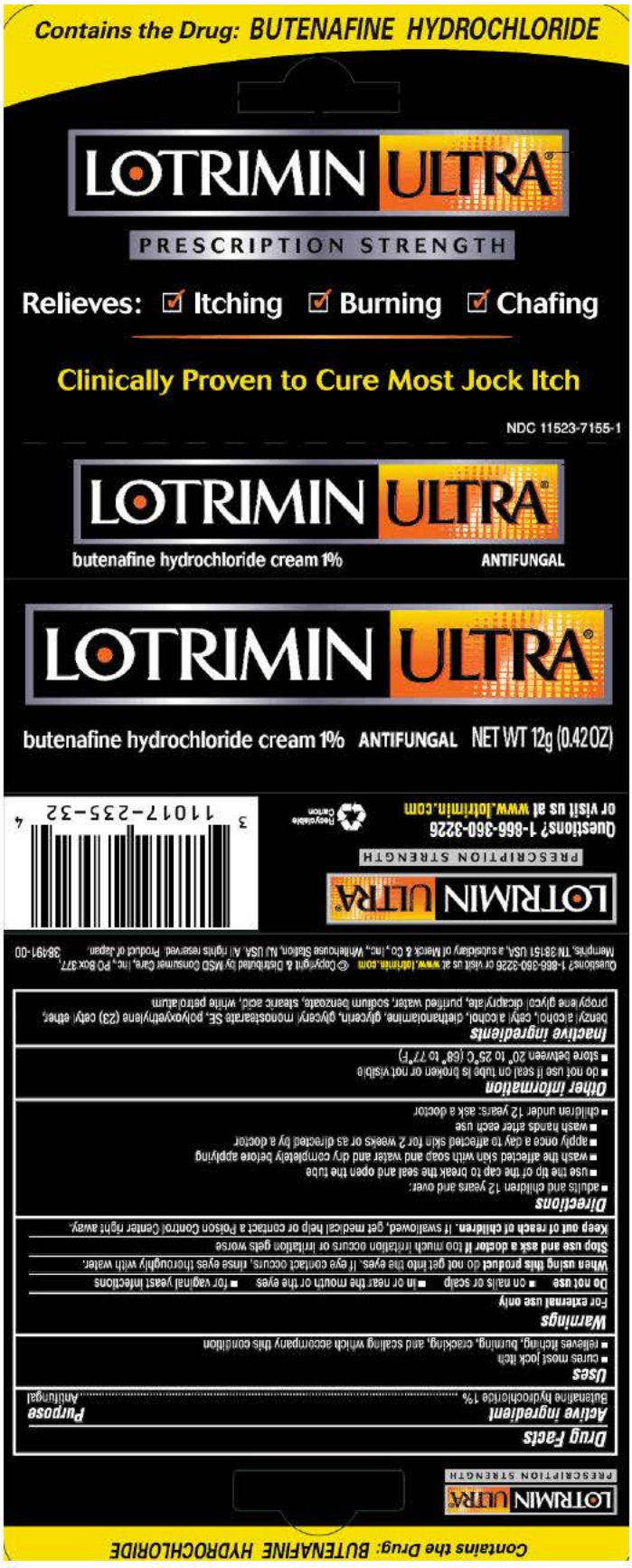
When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or irritation gets worse

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions ■ adults and children 12 years and older: ■ use the tip of the cap to break the seal and open the tube ■ wash the affected skin with soap and water and dry completely before applying ■ apply once a day to affected skin for 2 weeks or as directed by a doctor ■ wash hands after each use ■ children under 12 years: ask a doctor

Do not use if seal on tube is broken or not visible. See crimp for lot number and expiration date. Store between 20° to 25°C (68° to 77°F). Questions? 1-866-360-3226 27974-06


Contains the Drug: BUTENAFINE HYDROCHLORIDE
LOTRIMIN ULTRA®
PRESCRIPTION STRENGTH
Relieves: ☑ Itching ☑ Burning ☑ Chafing
Clinically Proven to Cure Most Jock Itch
NDC 11523-7155-1
LOTRIMIN ULTRA®
butenafine hydrochloride cream 1% ANTIFUNGAL
LOTRIMIN ULTRA®
butenafine hydrochloride cream 1% ANTIFUNGAL NET WT 12g (0.42 OZ)
Questions? 1-866-360-3226
or visit us at www.lotrimin.com
Recyclable Carton
3 11017-235-32 4
LOTRIMIN ULTRA®
PRESCRIPTION STRENGTH
Drug Facts
Active ingredient
Butenafine hydrochloride 1%
Purpose
Antifungal
Uses
■ cures most jock itch
■ relieves itching, burning, cracking, and scaling which accompany this condition
Warnings
For external use only
Do not use ■ on nails or scalp ■ in or near the mouth or the eyes ■ for vaginal yeast infections
When using this product do not get into the eyes. If eye contact occurs, rinse eyes thoroughly with water.
Stop use and ask a doctor if too much irritation occurs or irritation gets worse
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions
■ adults and children 12 years and over:
■ use the tip of the cap to break the seal and open the tube
■ wash the affected skin with soap and water and dry completely before applying
■ apply once a day to affected skin for 2 weeks or as directed by a doctor
■ wash hands after each use
■ children under 12 years: ask a doctor
Other information
■ do not use if seal on tube is broken or not visible
■ store between 20° to 25°C (68° to 77°F)
Inactive ingredients
benzyl alcohol, cetyl alcohol, diethanolamine, glycerin, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether, propylene glycol dicaprylate, purified water, sodium benzoate, stearic acid, white petrolatum
Questions? 1-866-360-3226 or visit us at www.lotrimin.com © Copyright & Distributed by MSD Consumer Care, Inc., PO Box 377, Memphis, TN 38151 USA, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ USA. All rights reserved. Product of Japan. 38491-00
LOTRIMIN ULTRA®
PRESCRIPTION STRENGTH
Contains the Drug: BUTENAFINE HYDROCHLORIDE

MedWatch – None

2. **USP & PF** [Checked 3/13/14]: The DS and DP are not compendial.
3. **PATENT AND EXCLUSIVITY** [Checked 3/13/14]: None
4. **INACTIVE INGREDIENTS** [3.2.P.1 – Original submission]

   Below list is consistent with the information in the labeling.

Strength (Label claim)	1%			
Ingredient	**Quality Standard**	**Quantity (% w/w)**	**mg/g**	**Function**
Butenafine Hydrochloride	Taro	1.000	(b) (4)	Active Pharmaceutical Ingredient
White Petrolatum	USP	3.600		(b) (4)
Cetyl Alcohol	NF	5.000		
Stearic Acid	NF	5.000		
Glyceryl Monostearate SE	Taro	4.000		
Propylene Glycol Dicaprylate	Taro	10.000		
Purified Water	USP	62.200		
Glycerin	USP	6.000		
Polyoxyethylene (23) Cetyl Ether	Taro	2.000		
Trolamine	NF	0.500		
Sodium Benzoate	NF	0.200		
Benzyl Alcohol	NF	0.500		
Total theoretical weight	--	100.00	1000.0	---

5. **MANUFACTURING FACILITY** [3.2.P.3.1 – Original submission]

   Taro Pharmaceuticals Inc.

   (b) (4)

6. **FINISHED PRODUCT DESCRIPTION & PRODUCT LINE** [Per Drug Facts and DailyMed]

   RLD: Lotrimin Ultra® Athlete's Foot; 12 g, 15 g, 24 g, and 30 g tubes, and Lotrimin Ultra® Jock itch; 12 g and 15 g tubes.

   ANDA: Butenafine Hydrochloride Cream, 1% for Athlete's Foot; 12 g, 15 g, 24 g, and 30 g tubes Butenafine Hydrochloride Cream, 1% Jock itch; 12 g, 15 g, 24 g, and 30 g tubes.

   White cream [Per 3.2.P.1]

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS** [Per Drug Facts]

   RLD: Store between 20° to 25°C (68° to 77°F). Do not use if seal on tube is broken or not visible.

   ANDA: Same as RLD.

8. CONTAINER/CLOSURE [3.2.P.7.1 - Original submission]

The container/closure systems consist primarily of laminate High Density Polyethylene (HDPE) tube and white polypropylene (PP) cap.

12 gram: ¾" x 3-1/4" White laminate tube, EPK-6456-0 with [redacted] (b) (4) cap

15 gram: ¾" x 4-1/4" White laminate tube, EPK-6458-0 with [redacted] (b) (4) cap

24 gram: 7/8" x 4" White laminate tube, EPK-6461-0 with [redacted] (b) (4) cap

30 gram: 1" x 4" White laminate tube, EPK-6463-0 with [redacted] (b) (4) cap

9. RELATED APPLICATIONS: None

10. CITIZEN PETITION: None

Date of Review:	3/17/2014
Primary Reviewer:	Ellen Hwang
Team Leader:	John F. Grace

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

/s/

ELLEN E HWANG
03/20/2014

THUYANH VU on behalf of JOHN F GRACE
03/21/2014
for Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

CHEMISTRY REVIEWS

First Generic
CMC-Approvable

Recommendation:
ANDA:
☒ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☐ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 205181

Amendment Review CR #3b

Drug Name/Dosage Form	Butenafine Hydrochloride Cream
Strength	1%
Reviewer(s)	Mamta Kapoor, Ph.D.
Applicant	Taro Pharmaceuticals USA, Inc.
RLD	NDA 021307 -Lotrimin Ultra® (Butenafine Hydrochloride) Cream 1%; by Bayer HealthCare LLC

SUBMISSION(S) REVIEWED	**DOCUMENT DATE**
SD#9, eCTD 0008, Quality/Response to Information Request	06/01/2017

Previous Submissions Reviewed	**Document Date**
SD#8, eCTD 0006, Quality/Response to Information Request	03/10/2017
SD#7, eCTD 0007, Administrative change (update on US agent)	03/03/2017
SD #6, Resubmission/After Action- Complete; Quality/Quality Information	11/16/2016
SD #5, Quality/Response To Information Request	09/12/2016
SD #4 Quality Amendment	06/03/2016
SD #3 Quality/Response to Information Request	07/30/2015
SD #2 Quality Amendment	08/15/2013
Original Submission	02/04/2013

DMFs: updates in blue

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
019551	Taro Pharmaceutical Industries LTD	Butenafine Hydrochloride	Adequate	05/25/2017	Xianru Sun
(b) (4)			N/A		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Adequate	01/04/2017	Charles Hoppes
Bioequivalence	Adequate	09/26/2014	Sunny Tse
Toxicology/Clinical	N/A		
EA	Request for Exclusion provided in Module 1.12.14		Shin (Grace) Chou
Radiopharmaceutical	N/A		
Samples Requested	N/A		

FACILITIES:

Overall Recommendation: Approve			
Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			

Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Drug Product Manufacturer	*Taro Pharmaceuticals, Inc 130 East Drive, Brampton, Ontario, Canada.*	3002808384/9614240	Approve facility
			(b) (4)

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(b) (4)

[redacted]

Labeling & Package CMC Related Concerns: N/A

Overall Reviewer's Assessment and Signature:

CMC is adequate as per this review.

Mamta Kapoor, Ph.D., 06/05/2017

Secondary Review Comments and Concurrence:
Concur. The firm has addressed all CMC concerns and the ANDA is CMC approvable.

Chandan M Thomas, 06/08/2017

List of Deficiencies To Be Communicated by Information Request:

Drug Substance
N/A

Drug Product:
N/A

Labeling:
N/A

Mamta Kapoor

Digitally signed by Mamta Kapoor
Date: 6/29/2017 10:33:31AM
GUID: 54a2e25f000678567e4c58aaef83a8f5

Chandan Thomas

Digitally signed by Chandan Thomas
Date: 6/09/2017 10:52:25AM
GUID: 5316073500008324e37074a6ef302889

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☒ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 205181

Amendment Review CR #3

Drug Name/Dosage Form	Butenafine Hydrochloride Cream
Strength	1%
Reviewer(s)	Shin Grace Chou
Applicant	Taro Pharmaceuticals USA, Inc.
RLD	NDA 021307 (Lotrimin Ultra Cream; by Schering Plough HealthCare Products)

SUBMISSION(S) REVIEWED	DOCUMENT DATE
SD #4 Quality Amendment	06/03/2016

DMFs:

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
19551	Taro Pharmaceutical Industries LTD	Butenafine Hydrochloride	Adequate New quality amendment and annual report submitted 08/22/2016 pending review	01/15/2016	Last reviewed by Weixiang Dai
(b) (4)			N/A		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Deficient	7/29/2016	Charles Hoppes
Bioequivalence	Adequate	06/25/2014	Sunny Tse
Toxicology/Clinical	N/A		
EA	Request for Exclusion provided in Module 1.12.14		Shin Grace Chou
Radiopharmaceutical	N/A		
Samples Requested	N/A		

FACILITIES:

Overall Recommendation: Pending			
Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			
Drug Product			

Function	Site Information	FEI/CFN#	Status
Taro Pharmaceuticals, Inc *Drug Product Manufacturer*	*130 East Drive,* *Brampton, Ontario,* *Canada.*	3002808384/9614240	Acceptable through 02/08/2016

(b) (4)

[redacted]

24 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ICH Q1A(R2) guidance.

Labeling & Package CMC Related Concerns: N/A

Overall Reviewer's Assessment and Signature: Not Approvable – minor
Shin Grace Chou, 08/28/2016

Secondary Review Comments and Concurrence: Not Satisfactory

P. Onyimba, 9/15/2016

List of Deficiencies To Be Communicated by Information Request or Complete Response:

1. (b) (4)

2. We acknowledge your assertion that the proposed product is deemed bioequivalent via a clinical endpoint bioequivalence study. We further acknowledge your commitment to develop a validated in vitro method in the future to support post approval changes, if warranted. However, without initial validated in vitro release method and the corresponding in vitro release data for the proposed product, we will have no basis to evaluate and identify the changes in product quality and performance for future formulation and process changes. We remind you that a validated in-vitro release method and the corresponding in-vitro release results for your proposed drug product may be required to support any future post approval changes. Please acknowledge.

3. (b) (4)

(b) (4)

4.

5.

Patricia Onyimba

Digitally signed by Patricia Onyimba
Date: 9/19/2016 11:39:02AM
GUID: 508da700000286b9cc83ab8591f4d600

Shin Chou

Digitally signed by Shin Chou
Date: 9/19/2016 11:36:16AM
GUID: 51defe4b00010821ff38f29e384b0ab5

First Generic
Not Approvable – Minor

ANDA 205181

Butenafine Hydrochloride Cream 1%

Taro Pharmaceuticals USA, Inc.

Shin Grace Chou, PhD
OGD/DC1
Review #1

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #205181**

2. **REVIEW #: 1**

3. **REVIEW DATE: 06/09/2014**

4. **REVIEWER: Shin Grace Chou, PhD**

5. **PREVIOUS DOCUMENTS: None**

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original Submission	02/04/2013
Quality Amendement	08/15/2013

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Taro Pharmaceuticals USA Inc
Address:	3 Skyline Drive, Hawthorne, NY 10532
Representative:	Kavita Srivastava, Executive Director of Regulatory Affairs
Telephone:	(914)345-9001 ex (b) (6)

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: None
Non-Proprietary Name (USAN): Butenafine Hydrochloride

9. **LEGAL BASIS FOR SUBMISSION:**

- Reference listed drug (RLD): Lotrimin Ultra
- NDA#: 021307
- RLD's Firm's name: Schering Plough HealthCare Products
- Patent (S): No unexpired patent
- Exclusivity: No unexpired exclusivity

10. **PHARMACOL. CATEGORY:**

- antifungal agent used in the topical treatment of athlete's foot, jock itch and ringworm. Tinea corporis and tinea pedis (interdigital)

11. **DOSAGE FORM: Cream**

12. **STRENGTH/POTENCY: 1%**

13. **ROUTE OF ADMINISTRATION: Topical (Cutaneous)**

14. Rx/OTC DISPENSED: OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ☒ **Not a SPOTS product**

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☒ Not a NANO product

15c. PRECEDENT:

☐ The review of this ANDA establishes a precedent – TL concurrence

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

(a) Recommended International Non-proprietary name (INN):
Butenafine Hydrochloride

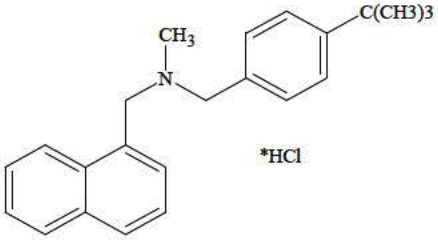
Chemical names (IUPAC):

- N-{[4-(1,1-Dimethylethyl)phenyl]methyl}-N-methyl-1-naphthalenemethanamine hydrochloride
- N-(*p-tert*-butylbenzyl)-N-methyl-naphthalenemethylamine hydrochloride

Other non-proprietary name(s) (e.g., national name, USAN, BAN, etc.):
Butenafine Hydrochloride (INN); BUT.HCl; But-HCl

Chemical Abstracts Service (CAS) registry number:
CAS# [101827-46-7]
CAS# [101828-21-1], for the free base

(b) Molecular structure, including relative and absolute stereochemistry:



(c) Molecular formula: $C_{23}H_{27}N \cdot HCl$

(d) Molecular weight: 353.93 g/mole (317.47 g/mole for the free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
19551	Taro Pharmaceutical Industries LTD	Butenafine Hydrochloride	Deficient	09/17/2014	Weixiang Dai
[redacted] (b) (4)			N/A		

[1] 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
Approved IND	42762	Penederm's IND for Butenafine HCl cream 1%
Approved NDA	021307	Designated as RLD (Rx to OTC)
Approved NDA	020663	Legacy type 6 application (new indication)
Approved NDA	020524	Original Rx (Mentax Cream)
Approved NDA	021408	Mentax-Tc (never launched, discontinued)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Deficient	03/21/2014	Ellen Hwang
Bioequivalence	Adequate	06/25/2014	Sunny Tse
Toxicology/Clinical	N/A		
EA	Request for Exclusion provided in Module 1.12.14		
Radiopharmaceutical	N/A		
Samples Requested	N/A		

19. ORDER OF REVIEW

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

20. EES INFORMATION

Overall Recommendation: Pending			
Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Taro Pharmaceuticals, Inc Drug Product Manufacturer	*130 East Drive, Brampton, Ontario, Canada.*	3002808384/9614240	Acceptable through 02/08/2016
(b) (4)			

Chemistry Review for ANDA 205181

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This ANDA is currently not approvable. The DMF, labeling, and CMC reviews are deficient. Clinical bioequivalence is deemed adequate. The EES recommendation is acceptable.

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)

I Drug Substance

The drug substance butenafine hydrochloride is manufactured by Taro pharmaceuticals. The drug substance is a white crystalline powder with a molecular weight of 353.93g/mol. The crystal is freely soluble in methylene chloride, chloroform, and methanol; sparingly soluble in ethanol and 2-propanol (IPA); slightly soluble in acetone and water; and practically insoluble in toluene. There is no official USP monograph for butenafine hydrochloride drug substance, but there is a monograph for the drug substance in the Japanese Pharmacopeia. Butenafine hydrochloride exists in only one polymorphic form, and there is no chiral center in this drug substance. The butenafine hydrochloride drug substance used in this ANDA is described in DMF #19551.

II Drug Product

The reference listed drug (RLD) for the proposed drug product is an over the counter (OTC) drug product Lotrimin Ultra (NDA 21307) marketed by Schering-Plough Healthcare Products. The OTC product is the subject of marketed Rx product for Mantex (butenafine HCl) cream, 1% (NDA 20524 and subsequently NDA 20663) marketed by Penederm. The subject of the present ANDA butenafine hydrochloride cream, 1% is manufactured by Taro Pharmaceuticals Inc. (Brampton, Ontario, Canada), and distributed by Taro Pharmaceuticals U.S.A., Inc. (3 Skyline Drive, Hawthorne, New York, USA). Most of the CMC specifications in NDA 20663 and the subsequent OTC conversion in NDA 21307 refer back to the drug product standard set forth in the original NDA 20524, but a number of impurities stability specifications have relaxed over the years, with the consent of pharm/tox consult.

The reference listed drug for this application is Lotramin Ultra (Butenafine HCl Cream 1%), and there is no official monograph in the USP or CFR for the drug product. Butenafine HCl Cream 1% is a topical antifungal agent indicated for the

treatment of interdigital tinea pedis (NDA 20524) and tinea corporis and cruis (NDA 20663).

Each gram of butanefine HCl cream 1% contains butanefine hydrochloride, cetyl alcohol, glyceryl monostearate SE, polyoxyethylene (23) cetyl ether (b) (4) propylene glycol dicaprylate, stearic acid, white petrolatum, glycerine, trolamine, benzyl alcohol, sodium benzoate, and water. The RLD product and the formulation of the proposed drug product contain similar excipients that are widely used in topical emulsion drug and cosmetic products. However, the (b) (4), diethanolamine, used in RLD, was replaced with triethanolamine (trolamine) in the Taro proposed drug product due to the potential carcinogenic property of diethanolamine. The triethanolamine to trolamine replacement is deemed acceptable, for the trolamine was used in another previously approved butenafine HCl 1% cream, Mentax-Tc (NDA 21408), which consists of a slightly improved formulation from the Rx version of the RLD drug product, Mentax.

(b) (4)

The exhibit batch was manufactured and packaged into the 12 g, 15 g, 24 g and 30 g laminate tubes and placed on stability under accelerated and room temperature conditions. The proposed expiration dating period is two years at room temperature. This is supported by the stability data.

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

Route of Administration	Topical
Proposed Indication(s)	Antifungal agent used in the treatment of athlete's foot, jock itch and ringworm

Dosing Regime	• use the tip of the cap to break the seal and open the tube • wash the affected skin with soap and water and dry completely before applying • apply once a day to affected skin for 2 weeks or as directed by a doctor • wash hands after each use

(b) (4)

[redacted]

C. Initial and Updated Risk Assessment

Risk Identification FMECA – ANDA 205-181, Butenafine Hydrochloride Cream, 1%

PRODUCT PROPERTY/CQA	(O)	(S)	(D)	RPN	Comments	Updated risk	Comments
Assay (Active)	2	3	3	18			No concerns noted at release and on stability
Assay (Antimicrobial preservative)	2	3	3	18	(O) Formulation contains sodium benzoate and benzyl alcohol (b) (4).		No concerns noted. (b) (4) [redacted]
Chemical Stability (All CQAs)	1	3	4	12	(O) No significant trending through 12 months at long term storage condition.		No significant trending through long term storage stability data. Further assessment pending
Bulk Content Uniformity	3	4	3	36	(O) Drug product is a cream emulsion.		No content uniformity test. See deficiency 13.

Risk Identification FMECA – ANDA 205-181, Butenafine Hydrochloride Cream, 1%

PRODUCT PROPERTY/CQA	(O)	(S)	(D)	RPN	Comments	Updated risk	Comments
Uniformity in Containers (includes USP <905> for single-dose)	3	3	3	27	(O) Drug product is a cream emulsion.		Uniformity in the container is included in the release (homogeneity test) and stability specification
Microbial Limits	3	2	3	18			Microbial testing conducted in accordance with USP <1111> acceptance criteria.
Weight Loss	2	3	3	18			Not tested. See deficiency 23
Attributes Related to Q3/Arrangement of Matter							
pH	3	3	3	27			Comparability between generic and RLD demonstrated. See P.2
Viscosity	4	3	4	48	(O) Drug product is a cream emulsion.		The product is not Q1/Q2. The viscosity among different batches has been consistent. No concerns noted at release or stability
Physical Stability (API solid state in drug product)	N/A- Drug substance is fully dissolved in the cream emulsion. No evidence of crystals or precipitation reported during development. The RLD proposed doing						
Physical Stability (Phase Separation/Sedimentation)	4	4	3	48	(O) Drug product is a cream emulsion.		No issues noted in the stability data.
Physical Stability (API Precipitation)	2	4	4	32	(b) (4)		(b) (4)
Drug Release Rate	3	4	4	48			(b) (4)
Particulate Size (for multi-phasic semi-solid products (e.g. emulsions, microspheres, liposomes, etc.))	4	4	4	64	(b) (4)		
Type of emulsion (e.g. o/w, w/o, w/o/w, o/w/o, o/w microemulsions, etc.)	4	4	4	64			

D. Basis for Approvability or Not-Approval Recommendation

This ANDA is currently not approvable. The DMF, labeling, and CMC reviews are deficient. The EES recommendation is acceptable. The initial risk identified for this ANDA was not mitigated to an acceptable level.

(b) (4)

23. [redacted]

24.

25.

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

1. Please include all available updated stability data for all batches manufactured to date.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shin Grace Chou, 09/15/2014
Chemistry Team Leader Name/Date: Derek Smith, 09/16/2014
Project Manager Name/Date: Hany S Edward/9/25/14
DD/DDD Name/Date:

TYPE OF LETTER:

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

/s/

SHIN G CHOU
09/25/2014

HANY S EDWARD
09/25/2014

DEREK S SMITH on behalf of JAMES M FAN
09/26/2014

BING CAI
09/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

BIOEQUIVALENCE REVIEWS

Addendum to Review of a Clinical Endpoint
Bioequivalence Study Following OSI Inspection Results

Drug Product:	Butenafine Hydrochloride Topical Cream, 1%
Drug Class:	Fungicides/Antidermatophyte Agents
Chemical Name:	butenafine hydrochloride (N-4-tert-butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride)
ANDA:	205181
ANDA Applicant:	Taro Pharmaceuticals U.S.A., Inc.
Reference Listed Drug:	Lotrimin Ultra® (OTC product)
NDA:	021307 (approved on 12/7/01)
RLD Applicant:	MSD Consumer Care Inc.
Primary Reviewer:	Sunny Tse, Ph.D. Clinical Reviewer Division of Clinical Review Office Generic Drugs
Secondary Reviewer:	Carol Y. Kim, Pharm.D. Acting Team Leader, ANDA Team Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
Tertiary Reviewer:	Lesley-Anne Furlong, M.D. Acting Director Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
Materials Reviewed:	Original Submission: 2/4/13 Study Amendment: none FDA Statistical Reviews: 6/12/14 (prior to OSI inspection result) and 9/23/14 (after OSI inspection result) OSI Inspection Report: 9/9/14 DCR original review without OSI inspection result: 6/25/14
Date of Original Submission:	2/4/13
Date of Completion:	9/25/14
Conclusion:	**From DCR perspective, the approval is recommended. According to the FDA statistical re-analysis, excluding one subject (b) (6) based on the OSI recommendation, the study outcome remains the same.**

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Addendum to Review of a Clinical Endpoint Bioequivalence Study for ANDA 205181

1 Executive Summary

Following exclusion of one subject (b) (6) from the clinical site #6, based on OSI recommendation, the double-blind, randomized, multi-center, parallel-group study (BTNF 1104) in the treatment of interdigital tinea pedis demonstrates that Taro Pharmaceuticals U.S.A., Inc.'s Butenafine Hydrochloride Topical Cream, 1%, is bioequivalent to the reference listed drug (RLD), MSD Consumer Care Inc.'s Over the Counter Product (OTC) Lotrimin Ultra® (Butenafine Hydrochloride Cream), 1% (NDA 021307, approved on 12/7/01).

Based on the FDA statistical re-analysis, excluding one subject (b) (6) per OSI recommendation, a total of 501 subjects were included in the FDA Modified Intent-to-Treat population (MITT)[1] population and 455 subjects were included in the FDA Per Protocol (PP)[2] population. The FDA statistical reviewer concludes that the 90% Confidence Interval (CI) of the difference in therapeutic cure rates between the test product and reference product in the FDA per-protocol (PP) population at the test-of-cure visit (study Day 38-46) is [-0.009, +0.17], within the bioequivalence limits of [-0.20, +0.20]. The FDA statistical reviewer also confirms that both test and reference products are shown to be superior to the vehicle ($p<0.0001$) in the final FDA MITT population. Therefore, the study outcome remains the same.

1.1 Approval Recommendation

Following the OSI inspection results, the clinical data submitted to ANDA 205181 (BTNF 1104) are adequate to demonstrate bioequivalence of Taro Pharmaceuticals U.S.A., Inc.'s Butenafine Hydrochloride Topical Cream, 1%, with the reference listed drug, MSD Consumer Care Inc.'s Lotrimin Ultra® (Butenafine Hydrochloride Cream), 1%. Therefore, from the DCR perspective, the test product is recommended for approval. **This conclusion is based on information available after OSI inspection findings.**

1.2 Summary of OSI Inspection Findings (9/9/14)

A. Review of the Office of Scientific Investigation (OSI) Report: 9/9/14
At the conclusion of the inspection of three clinical sites (#12, 15, and 06) in US, a FDA Form

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[1] The applicant's definition of the mITT population is consistent with the product draft guidance: Subjects who were enrolled in the study and met all inclusion/exclusion criteria, had a positive baseline skin fungal culture for *T. rubrum, T. mentagrophytes, T. tonsurans, or E. floccosum*, applied at least 1 dose of assigned study medication, and returned for at least 1 visit after Visit 1/Day 1. This population excluded subject (b) (6)

[2] Per Protocol population: Subjects who were enrolled in the study and met all inclusion/exclusion criteria, had a positive baseline skin fungal culture for *T. rubrum, T. mentagrophytes, T. tonsurans, or E. floccosum*, did not take any concomitant medications prohibited by the protocol or have any other significant protocol violations, and returned for Visit 3/Day 42 (± 4 days) within the designated visit window with a compliance rate between 75% and 125% (at least 11 applications and no more than 17 applications). This population excluded subject (b) (6)

483 was issued at site #06 only. OSI recommended data from one subject (b) (6) from the clinical site #06 not be accepted for the review. Data from the remaining subjects at site #06 and all subjects from sites #12 and 15 were acceptable for the review.

Finding from site #06 (Lower Extremity Research)

Specific comments by the OSI inspector are shown below.

1. **An investigation was not conducted in accordance with the investigational plan. Specifically, per protocol inclusion criteria # 5, clinical assessment scores at the target site must include 2 for erythema and at least 2 for scaling or pruritus. Clinical assessment completed for Subject (b) (6) and documented on source document form at study baseline visit dated 6/19/2012, shows a score of 1 for both pruritus and scaling. This subject was initially reported and subsequently confirmed on a data correction form dates 10/11/2012 as meeting inclusion criterion # 5.**

Reviewer's Comments: *The OSI inspector noted altering source records without supporting documentation and stated that "the data generated from the subject (b) (6) are unreliable and should be excluded from the bioequivalence assessment". Based on the OSI recommendation, subject (b) (6) from site #06 was recommended to be excluded from the final FDA statistical analysis.*

2 Additional Clinical Review

2.1 Review of the FDA Statistical Report (addendum dated 9/23/14 after OSI inspection result)

The FDA addendum statistical review dated 9/23/14 is based on information following the OSI inspection findings (see OSI inspection report dated 9/9/14 for details). The conclusion of the FDA statistical re-analysis remains the same and the study demonstrates bioequivalence of the test and the reference products.

The summary of FDA addendum statistical review is shown below:

Bioequivalence: Primary Endpoint

Table 2: Proportion of Subjects with Therapeutic Cure at Visit 3/Day 42 (±4 days) in the FDA PP Population (excluding subject (b) (6)

Table 2: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the FDA's PP Population

	Treatment Group			90% CI for Bioequivalence
	Test	Reference	Vehicle	
FPP Population				
N	176	191	88	
Cure	102 (57.95%)	95 (49.74%)	13 (14.77%)	(-0.87,17.30)
No cure	74 (42.05%)	96 (50.26%)	75 (85.23%)	

Superiority

Table 3: Proportion of Subjects with Therapeutic Cure at Visit 3/Day 42 (±4 days) in the FDA mITT Population (excluding subject (b) (6)

Table 3: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the FDA's mITT Population

	Treatment Group			P-value for Superiority	
	Test	Reference	Vehicle	Test vs Vehicle	Reference vs. Vehicle
FITT Population					
N	194	208	99		
Cure	108(55.67%)	101(48.56%)	14(14.14%)	<.0001*	
No cure	86(44.33%)	107(51.44%)	85(85.86%)		<.0001*

*results from both Fisher's exact and approximate Z tests

Reviewer's Comment: *After excluding 1 subject based on OSI recommendation, the applicant's study demonstrates bioequivalence between products. The study outcome of the primary endpoint remains the same as the original DCR review of ANDA 205181 dated 6/25/14.*

2.2 Conclusion and Recommendation

2.2.1 Conclusion

After excluding (b) (6) subject based on OSI inspection findings, the clinical data presented in this ANDA 205181 demonstrate that Taro Pharmaceuticals U.S.A., Inc.'s Butenafine Hydrochloride Topical Cream, 1%, is bioequivalent to the reference listed drug, OTC Product Lotrimin Ultra® (Butenafine Hydrochloride Cream), 1%. The FDA addendum statistical review dated 9/23/14 supports that the 90% CI of the difference in therapeutic cure rates between the test product and reference product in the FDA PP population at the test-of-cure visit (study Day 38-46) is within the bioequivalence limits of [-0.20, +0.20]. Both test and reference products show superiority over the vehicle in the FDA MITT population, demonstrating that the study is sensitive enough to detect the difference between products. Therefore, the study outcome remains the same.

2.2.2 Recommendations

From DCR perspective, this application is recommended for approval, contingent on approval recommendations from the other disciplines on the review team.

CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has no comments to provide to the applicant.

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

/s/

SUNNY Y TSE
09/26/2014

CAROL Y KIM
09/26/2014

LESLEYANNE FURLONG
09/26/2014

Clinical Review of ANDA 205181
Bioequivalence Study with Clinical Endpoints

Drug Product:	Butenafine Hydrochloride Cream, 1%
Drug Class:	Fungicides/Antidermatophyte Agents (Topical) (4020120)
Chemical Name:	**butenafine hydrochloride** (N-4-tert-butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride)
ANDA:	205181
ANDA Sponsor:	Taro Pharmaceuticals U.S.A., Inc.
Reference Listed Drug:	Lotrimin Ultra®
NDA:	021307
RLD Sponsor:	MSD Consumer Care Inc.
Reviewer:	Sunny Tse, Ph.D. Clinical Reviewer Division of Clinical Review Office Generic Drugs
Secondary Reviewer:	Sarah H. Seung. Pharm.D. Clinical Reviewer Division of Clinical Review Office Generic Drugs
Tertiary Reviewers:	John R. Peters, MD Director, Division of Clinical Review Office of Generic Drugs Dale P. Conner, Pharm.D. Director, Division of Bioequivalence I Office of Generic Drugs
Materials Reviewed:	FDA Statistical Review finalized on 06/12/2014 by Yu-te Wu, Ph.D.
Guidance/Draft Guidance:	Draft Guidance on Butenafine HydrochlorideCream/Topical, 1%
Date Posted:	March 2012
Date of Original Submission:	02/04/2013
Addenda to submission:	08/15/2013
Date of Completion:	06/19/2014
Conclusion:	Recommend approval, pending satisfactory OSI inspection.

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Review of a Bioequivalence Study with Clinical Endpoint for ANDA 205181

1 Executive Summary

On 02/04/2013, Taro Pharmaceuticals U.S.A., Inc. submitted an abbreviated new drug application (ANDA) for Butenafine Hydrochloride Cream, 1%. In support for the ANDA, the sponsor conducted a clinical endpoint bioequivalence study (Study BTNF 1104). Study BTNF 1104was double-blinded, randomized, multi-center, parallel-group, placebo controlled for the treatment of interdigital tinea pedis. Study BTNF 1104, conducted between 01/12/2012 to 08/22/2012, compared the 1% strength of their proposed test product (Butenafine Hydrochloride Cream) to the reference listed drug (RLD), MSD Consumer Care Inc.'s Lotrimin Ultra® (Butenafine Hydrochloride Cream), 1% (Reference). The test and reference products were also compared to placebo (the vehicle).

1.1 Approval Recommendation

The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved therapeutic cure at Visit 3/Day 42, the Test-of-cure visit, which is 5 weeks after the end of 1 week treatment. Therapeutic cure was defined as having both clinical cure and mycological cure. Clinical cure was defined as a total signs and symptoms score of no more than 2 with no individual severity score greater than 1 on a 4-point scale (from 0 = none to 3 = severe). Mycological cure was defined as a negative KOH wet mount and a negative fungal culture. Based on information available prior to OSI inspection findings, the data submitted to ANDA 205181 are adequate to demonstrate bioequivalence of the sponsor's Butenafine Hydrochloride Cream, 1% with the RLD, MSD Consumer Care Inc.'s Lotrimin Ultra® (Butenafine Hydrochloride Cream), 1%. Therefore, from a clinical bioequivalence perspective, the test product is recommended for approval, pending satisfactory OSI inspection.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Butenafine Hydrochloride Cream, 1% is a product containing a synthetic antifungal agent. Lotrimin Ultra® is indicated for the topical treatment of athlete's foot between the toes, jock itch, and ringworm. The sponsor conducted a clinical endpoint bioequivalence study to establish the bioequivalence of their proposed Butenafine Hydrochloride Cream, 1% to the RLD, Lotrimin Ultra® (1%), in the treatment of interdigital tinea pedis. This was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study. Planned enrollment was 700 subjects to obtain about 475 modified intent-to-treat (mITT) subjects (190 per active treatment group and 95 for the vehicle group) and 405 per-protocol (PP) subjects (162 per active treatment group and 81 for the vehicle group). Subjects were instructed to apply a thin layer of study medication to cover the affected and immediately surrounding areas on one or both feet 2 times per day, morning and evening, for 7 consecutive days whether or not the area(s) appeared clinically healed (a total of 14 consecutive applications). Subjects were instructed not to dose within 4 hours of a scheduled

study visit. Subjects who met all of the inclusion and none of the exclusion criteria were randomized in a 2:2:1 ratio to Test, Reference, or Vehicle treatment, respectively.

1.2.2 Comparative Efficacy

The recommended primary endpoint of the study is the proportion of subjects with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit conducted 5 weeks (+/- 4 days) after the end of treatment, (study Day 38-46). Mycological cure is defined as a negative KOH test AND a negative fungal culture. Clinical cure is defined as a total severity score no more than 2 with no individual severity score greater than 1, on a 4-point scale provided. To establish bioequivalence, the 90% confidence interval of the difference in therapeutic cure rates between the test product and reference product at the test-of-cure visit (study Day 38-46) must be within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the per-protocol (PP) population.

The FDA's statistical analysis shows the 90% CI of the difference in therapeutic cure rates between the test product (58.2%) and reference product (49.7%) at the test-of-cure visit (study Day 38-46) was (-0.61%, 17.52%), within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population.

The test (55.9%) and reference (48.56%) products were both superior over vehicle (14.14%) in the FDA's mITT population with $p<0.0001$.

1.2.3 Comparative Safety

The safety data submitted in this ANDA confirmed that the test product did not cause any worse treatment emergent adverse events (TEAEs) compared to the reference product in the topical treatment of interdigital tinea pedis. A brief summary is provided below.

	Total (N=707)	Test (n=283)	RLD (n=283)	Placebo (n=141)	Comment
Patients with at least one TEAEs	36 (5.1%)	12 (4.2%)	16 (5.7%)	8 (5.7%)	• p>0.5 (test vs. RLD) • ≤ 2 SAEs or deaths were reported in any group
Discontinued study drug due to above TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Severity (Patients with at Least One TEAE)					
Mild	21 (3.0%)	8 (2.8%)	8 (2.8%)	5 (3.5%)	
Moderate	13 (1.8%)	4 (1.4%)	6 (2.1%)	3 (2.1%)	
Severe	2 (0.3%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Relationship to Study Medication (Patients with at Least One TEAE)					
Related	4 (0.6%)	1 (0.4%)	3 (1.1%)	0 (0.0%)	
Unrelated	32 (4.5%)	11 (3.9%)	13 (4.6%)	8 (5.7%)	

2 Clinical Review

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Drug Product	Butenafine Hydrochloride Cream, 1%
Drug Class	Fungicides/Antidermatophyte Agents (Topical) (4020120)
Reference Listed Drug	Lotrimin Ultra®
RLD Firm	MSD Consumer Care Inc.
NDA #	021307
Date of RLD Approval	12/07/2001
Approved Indication(s)	athlete's foot between the toes, jock itch, and ringworm

Recommended Dosing Regimens	**athlete's foot between the toes:** apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor **jock itch and ringworm:** apply once a day to affected skin for 2 weeks or as directed by a doctor
Description of the reference drug, including pertinent safety or dosing considerations	**Butenafine Hydrochloride** Butenafine HCl is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The benzylamine derivatives, like the allylamines, act an earlier step in the ergosterol biosynthesis pathway than the azole class of antifungal drugs. Depending on the concentration of the drug and the fungal species tested, butenafine HCl may be fungicidal or fungistatic in vitro. However, the clinical significance of these in vitro data is unknown.

2.1.1.1 Brief discussion about the indication and reference drug

Athlete's foot, also known as tinea pedis, is a superficial infection caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum*, or other causative dermatophytes. *T. rubrum* is the most common causative organism in tinea pedis and, therefore, it is anticipated that at least 50% of the subjects will have fungal culture positive for *T. rubrum*.

Over-the-counter Lotrimin Ultra® contains Butenafine Hydrochloride (HCl) Cream, 1%, a benzylamine derivative with a mode of action similar to that of the allylamine class of antifungal drugs. Butenafine HCl is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The benzylamine derivatives, like the allylamines, act at an earlier step in the ergosterol biosynthesis pathway than the azole class of antifungal drugs. Butenafine HCl has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections: *E. floccosum, Malassezia furfur, T. mentagrophytes, T. rubrum, and T. tonsurans*. Taro Pharmaceuticals, Inc. has developed a generic formulation of Butenafine HCl Cream, 1%.

2.1.2 Regulatory Background

2.1.2.1 Regulatory History

Topical Butenafine Hydrochloride Cream, 1% is not one of the seven over-the-counter (OTC) topical antifungals listed in the final monograph first published in the FEDERAL REGISTER of September 23, 1993 (58 FR 49890) and later amended in the FEDERAL REGISTER of May 29,

2001 (66 FR 29059) for OTC topical antifungal drug products for human use (21 CFR Part 333).[1]

The Reference Listed Drug (RLD) for this test product, Lotrimin Ultra® Cream, 1% (NDA 021307) was approved on December 7, 2001. NDA 021307 indications are athlete's foot between the toes, jock itch, and ringworm.

Draft Guidance on Butenafine Hydrochloride (NDA 021307) Cream/Topical, 1% (Mar 2012) was posted on the FDA webpage: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296737.pdf.

2.1.2.2 INDs, Protocols, or Control Documents submitted by Sponsor

On 1/10/2008, the sponsor submitted a protocol (P08-019) for the 1% strength. The sponsor's protocol (P08-019) was submitted to OGD prior to the posting of these Draft Guidances on Butenafine Hydrochloride. The sponsor was notified via letter dated 02/08/2012 regarding the DCR recommendations for protocol #P08-019. Comments forwarded to the sponsor in the 02/08/2012 letter are consistent with the recommendations found in the Draft Guidance corresponding to NDA 021307 for the test product.

2.1.2.3 INDs, Protocols, or Control Documents submitted by other sponsors

None

2.1.2.4 Previous ANDA submissions for same product

None

2.1.3 Other Relevant Information

In addition to Lotrimin Ultra® Cream, 1%, there are two approved prescription topical cream formulations of butenafine hydrochloride creams: Mentax® and Mentax-TC®.

Mentax® (butenafine HCl) Cream, 1% (NDA 020524) is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *M. furfur* (formerly *P. orbiculare*). Draft Guidance on Butenafine Hydrochloride (NDA 020524) Cream/Topical, 1% (Mar 2012) was posted on the FDA webpage: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296735.pdf

[1] The seven OTC topical antifungals listed in the monograph are clioquinol 3%, clotrimazole 1%, haloprogin 1%, miconazole nitrate 2%, povidone-iodine 10%, tolnaftate 1%, and undecylenic acid and its salts (calcium, copper, and zinc) for a total undecylenate concentration of 10-25%.

MENTAX®-TC (butenafine HCl) Cream, 1% (NDA 021408) is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum orbiculare*).
Draft Guidance on Butenafine Hydrochloride (NDA 021408) Cream/Topical, 1% (Mar 2012) was posted on FDA webpage:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296738.pdf

2.2 Description of Clinical Data and Sources

Protocol Number	BTNF 1104
Study Title	A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of a Generic Butenafine HCl Cream, 1 % and Reference Listed Lotrimin Ultra® (Butenafine HCl Cream, 1 %) and Compare Both Active Treatments to a Vehicle Control in the Treatment of Interdigital Tinea Pedis
CRO	**Organization** / **Role**: (b) (4)
Study Period	12 January 2012 to 22 August 2012 (first subject visit to last subject visit)

Study Centers, Principal Investigators and Enrollment

This was a multicenter study conducted at 20 sites in the United States.

Table 1: Study Centers

Site No.	Principal Investigator Site Address	Telephone	No. Enrolled
01	Jeffrey M. Adelglass, MD Research Across America 9 Medical Parkway Plaza 4, Suite 202 Dallas, TX 75234	972-241-1222	43
02	Joe Blumenau, MD Research Across America 9 Medical Parkway Professional Plaza 4, Suite 202 Dallas, TX 75234	972-241-1222	35
03	Suzanne Bruce, MD Suzanne Bruce and Associates The Center for Skin Research 1900 St. James Place, Suite 650 Houston, TX 77056	713-850-0240	44
04	Eduardo Tschen, MD, MBA Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	505-247-4220	29
05	Scott D. Clark, MD Longmont Clinic, PC 1925 W. Mountain View Avenue Longmont, CO 80501	303-776-8718	34
06	Robert P. Dunne, DPM Lower Extremity Research, LLC 2717 N. Wickham Road, Suite 4 Melbourne, FL 32935	321-253-6191	79
07	Francisco Flores, MD FXM Research Miramar 3000 SW 148th Ave. Suite 216 Miramar, FL 33027	954-430-1097	50
08	Michael T. Jarratt, MD DermResearch, Inc. 8140 N. Mopac, Bldg 3, Suite 120 Austin, TX 78759	512-349-9889	52
09	Terry M. Jones, MD J&S Studies, Inc. 1710 Crescent Pointe Pkwy College Station, TX 77845	979-774-5933	26
10	Steven E. Kempers, MD Minnesota Clinical Study Center 7205 University Avenue NE Fridley, MN 55432	763-571-4200	14
11	Samuel N. Lederman, MD Altus Research, Inc. 4671 S. Congress Avenue, Suite 100B Lake Worth, FL 33461	Telephone number not available in study report	7

Site No.	Principal Investigator Site Address	Telephone	No. Enrolled
12	Linda Murray, DO Radiant Research, Inc. 6010 Park Boulevard Pinellas Park, FL 33781	727-544-6367	55
13	Adnan Nasir, MD, PhD Wake Research Associates 3100 Duraleigh Road, Suite 304 Raleigh, NC 27612	919-781-2514	13
14	Michael J. Noss, MD Radiant Research, Inc. 11500 Northlake Drive, Suite 320 Cincinnati, OH 45249	513-247-5577	39
15	Richard A. Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, TX 78229	210-949-0807	59
16	Robert T. Matheson, MD Oregon Medical Research Center, PC 9495 SW Locust Street, Suite G Portland, OR 97223	503-245-1525	13
17	Douglas R. Schumacher, MD Radiant Research, Inc. 1275 Olentangy River Road, Suite 202 Columbus, OH 43212	614-294-3854	35
18	Heather Woolery-Lloyd, MD[1] Tory Sullivan, MD, PA 16100 NE 16th Avenue, Suite A N. Miami Beach, FL 33162	305-652-8600	54
19	Zoe Diana Draelos, MD Dermatology Consulting Services 2444 North Main Street High Point, NC 27262	336-841-2040	7
20	David C. Wilson, MD The Education and Research Foundation, Inc. 2095 Langhorne Road Lynchburg, VA 24501	434-847-8400	19

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission:

February 4, 2013 (Study BTNF 1104 for the 1% strength)

Study Amendments:

August 15, 2013 (eCTD Sequence 0001; Form 3674; Quality/Response To Information Request) – telephone amendment submitted

FDA Statistical Review:

FDA Statistical Review and Evaluation finalized on 06/12/2014 by Yu-te Wu, Ph.D.

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Office of Scientific Investigations (OSI) Report:

An OSI inspection was requested on 09/04/2013.[2]
At the time of this review, the inspection results are pending.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states:

"This study was conducted in compliance with US FDA regulations (21 CFR Parts 50, 54, 56, and 312), the ethical principles of the Declaration of Helsinki, all applicable International Conference on Harmonisation (ICH) guidelines, and all local laws and regulations concerning clinical studies. Prior to initiation of the study, each principal investigator signed Form FDA 1572, agreeing to conduct the trial in compliance with the protocol and according to Good Clinical Practice (GCP).
All personnel involved in the conduct of this study were qualified by education, training, and experience to perform their assigned responsibilities."

Reviewer's Comments:

The sponsor's study appears to be in compliance with accepted ethical standards.

2.3.4 Evaluation of Financial Disclosure

The sponsor submitted Form FDA 3454, certifying that the clinical investigators involved in this study did not have any financial arrangements, significant payments, proprietary interest or equity interest to report.

2.4 Review of a Clinical Endpoint Bioequivalence Study

2.4.1 Brief Statement of Conclusions

The recommended primary endpoint of the study is the proportion of subjects with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit (study Day 38-46) conducted 5 weeks (+/- 4 days) after the end of treatment,. Mycological cure is defined as a negative KOH test AND a negative fungal culture. Clinical cure is defined as a total severity score no more than 2 with no individual severity score greater than 1, on a 4-point scale provided. Based on the FDA's statistical analysis, this study demonstrates bioequivalence of the test product with the reference product. The proportion of patients with therapeutic cure for the

[2] DARRTS ANDA 205181 09/04/2013 FRM-CONSULT-09(Biopharmaceutical Inspections Request) Original-1 (Unknown)

Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo in both studies.

2.4.2 General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's clinical endpoint bioequivalence study (BTNF 1104) was reviewed to evaluate the bioequivalence of the test product and the reference product. The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved therapeutic cure at Visit 3/Day 42. Therapeutic cure was defined as having both clinical cure, which was defined as a total signs and symptoms score of no more than 2 with no individual severity score greater than 1 on a 4-point scale (from 0 = none to 3 = severe), and mycological cure, which was defined as a negative KOH wet mount and a negative fungal culture. The sponsor's proposed primary endpoint was evaluated for bioequivalence.

2.4.3 Detailed Review of Bioequivalence Study with Clinical Endpoints

2.4.3.1 Protocol Review

Sponsor's protocol #:	BTNF 1104
Title	A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of a Generic Butenafine HCl Cream, 1 % and Reference Listed Lotrimin Ultra® (Butenafine HCl Cream, 1 %) and Compare Both Active Treatments to a Vehicle Control in the Treatment of Interdigital Tinea Pedis
Objectives	The primary objective of this study was to determine the comparability of the safety and efficacy of a generic Butenafine HCl Cream, 1 % (test product) and Lotrimin Ultra® (the reference listed drug [RLD]) in subjects with interdigital tinea pedis. It was determined whether the efficacy of each of the 2 active treatments is superior to that of the vehicle cream (placebo).

2.4.3.1.1 Study Design

Overall Study Design and Plan

This was a randomized, vehicle-controlled, parallel-group, multicenter, double-blind study conducted in patients male or non-pregnant, non-lactating females at least 18 years of age with tinea pedis with lesions localized to the interdigital spaces or that was predominantly interdigital but could have extended to other areas of the foot. Seven hundred patients were enrolled in order to obtain at least 405 per-protocol (PP) patients (162 patients in each active treatment group and 81 patients in the Vehicle group).

Subjects were enrolled into the study after informed consent had been obtained and after all inclusion/exclusion criteria had been met. The most severely affected toe web was designated as the target lesion and followed at all subsequent visits. The target lesion was the most likely to produce fungal isolates for potassium hydroxide (KOH) and culture. Per Protocol Amendment 2, subjects must have had a minimum total tinea pedis signs and symptoms score of 4 at the target

lesion, with scores of at least 2 for erythema and at least 2 for scaling or pruritus (see Section 9.5.1.1.3 for the rating scale). Prior to that amendment, the total signs and symptoms score was required to be at least 6 and to include a minimum score of 2 for erythema and a minimum score of 2 for scaling. A positive KOH wet mount from the skin scraping of the target lesion was also required for study entry. Subjects were to be discontinued from the study and not required to return at Visit 3 if their baseline cultures were not positive for causative dermatophytes, i.e., *T. rubrum, T. mentagrophytes, T. tonsurans* (added in Protocol Amendment 2), or *E. floccosum*.

Each eligible subject was randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups: Test, Reference, or Vehicle, respectively. Subjects applied the study medication 2 times per day for 7 consecutive days. Subjects came to the study site for mycological and clinical evaluations at Visit 1/Day 1 (Baseline), Visit 2/Day 8 (+ 3 days, End of Treatment), and Visit 3/Day 42 (± 4 days, Test of Cure/End of Study) or at early discontinuation.

A KOH wet mount, a skin scraping for culture from the target lesion, and assessment of the severity of tinea pedis signs and symptoms were performed at each visit, or at early discontinuation. If a subject had a negative baseline culture and returned for an early discontinuation visit, mycology assessments and assessment of the severity of tinea pedis signs and symptoms were not required.

Efficacy variables included erythema, scaling, maceration, fissuring/cracking, pruritus, burning/stinging, KOH test result, and fungal culture result.

The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved therapeutic cure at Visit 3/Day 42. Therapeutic cure was defined as having both clinical cure, which was defined as a total signs and symptoms score of no more than 2 with no individual severity score greater than 1 on the 4-point scale, and mycological cure, which was defined as a negative KOH wet mount and a negative fungal culture.

Procedures and Observations:

The schedule of study procedures is shown in Table 2.

Table 2: Schedule of Study Procedures (per sponsor)

Visit Title Visit Number Scheduled Day Scheduling Window	Baseline Visit 1 Day 1 None	End of Treatment Visit 2 Day 8 (+3 days)	Test of Cure/End of Study/Early Discontinuation Visit 3 Day 42 (±4 days)	Unscheduled
Written Informed Consent	X			
Demographic Information	X			
Medical History	X			
Physical Examination (Including Vital Signs)	X			
Urine Pregnancy Test[1]	X		X	X
Prior Medication Review	X			
Diagnosis of Tinea Pedis[2]	X			
Identification of Target lesion	X			
Mycological Evaluations (KOH Wet Mount and Fungal Culture)	X	X	X[3]	X
Investigator Evaluation of Erythema, Scaling, Maceration, and Fissuring/Cracking	X	X	X[3]	X
Subject Evaluation of Pruritus and Burning/Stinging	X	X	X[3]	X
Inclusion/Exclusion Criteria Review	X			
Randomization	X			
Dispense Study Medication and Subject Diary	X			
Subject Instruction/ Compliance Review	X	X	X[4]	X[4]
First Study Medication Application at Study Site	X			
Adverse Events Assessment	X	X	X	X
Concomitant Medication Review		X	X	X
Study Medication and Subject Diary Return, Accountability		X	X[4]	X[4]
Schedule/Confirm Next Visit	X	X		X

[1] For women of childbearing potential (excluding women who were surgically sterilized or postmenopausal for at least 2 years)

[2] Clinical diagnosis and positive potassium hydroxide (KOH) wet mount preparation showing segmented fungal hyphae.

[3] For subjects who had a negative baseline culture and returned for an Early Discontinuation Visit, mycological evaluations and investigator and subject evaluations of signs and symptoms were not applicable.

[4] Collection of previously uncollected subject diary and assessment of compliance and/or study medication and recording of study medication accountability (if applicable).

Reviewer's Comments:

The sponsor's overall study design and plan is consistent with the product draft guidance. The Table 2: Schedule of Study Procedures *is acceptable.*

Study Population:

Inclusion Criteria:

1. Willing and able to provide and understand written informed consent for the study.

2. Healthy male or non-pregnant, non-lactating female and at least 18 years of age and older. This was changed by Protocol Amendment 3 and previously had been at least 12 years of age per Protocol Amendment 1.

3. Clinical diagnosis of tinea pedis with lesions localized to the interdigital spaces or that was predominantly interdigital but could have extended to other areas of the foot (the non-interdigital lesions should not have been hyperkeratotic, i.e., characteristic of moccasin-type tinea pedis).

4. Tinea pedis must have been provisionally confirmed at baseline by a positive KOH wet mount preparation showing segmented fungal hyphae.

5. Had a sum of the clinical signs and symptoms scores of the target lesion of at least 4, including a minimum score of 2 for erythema and a minimum score of 2 for scaling or pruritus (on a scale of 0 to 3 where 2 indicated moderate severity). Prior to Protocol Amendment 2, the sum was required to be at least 6 and to include a minimum score of 2 for erythema and a minimum score of 2 for scaling.

6. Currently in general good health with no clinically significant disease other than interdigital tinea pedis that might have interfered with the study evaluations.

7. Willing and able to understand and comply with the requirements of the study, including applying the medication as instructed, returning for the required treatment period visits, complying with therapy prohibitions, and able to complete the study.

8. Women of childbearing potential (excluding women who were surgically sterilized or postmenopausal for at least 2 years) must have had a negative urine pregnancy test and must have been willing to use an acceptable form of birth control during the study. The sponsor considered the following acceptable methods of birth control for this study: oral contraceptives, contraceptive patches, contraceptive implant, vaginal contraceptive, double barrier methods (e.g., condom and spermicide), contraceptive injection (Depo-Provera®), intrauterine device (IUD), hormonal IUD (Mirena®), and abstinence with a documented second acceptable method of birth control if the subject became sexually active. Subjects entering the study who were on hormonal contraceptives must have been on the method for at least 90 days prior to the study and continued the method for the duration of the study. Subjects who had used hormonal contraception and stopped must have stopped no less than 90 days prior to the study.

Reviewer's Comments:

Consistent with drug product draft guidance

Exclusion Criteria:

1. Females who were pregnant, breastfeeding, planning a pregnancy, or did not agree to use an acceptable form of birth control during the study.

2. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.

3. Presence of any other infection of the foot or other disease process that might have confounded the treatment evaluation.

4. History of dermatophyte infections unresponsive to systemic or topical antifungal drugs.

5. Known hypersensitivity to butenafine HCl or to any component of the study medications.

6. A subject must not have received any treatment listed in Table 3 more recently than the indicated washout period prior to Visit 1/Day 1 (Baseline).

Table 3: Prohibited Medications for Study Entry

Prohibited Medications	Washout Period Prior to Baseline
Antipruritics, including antihistamines	72 hours
Topical corticosteroid, antibiotic, or antifungal therapy	14 days (2 weeks)
Systemic (e.g., oral or injectable) corticosteroid, antibiotic, or antifungal therapy	30 days (1 month)
Oral terbinafine or itraconazole	60 days (2 months)
Immunosuppressive medication or radiation therapy	90 days (3 months)

7. Current oral, vaginal, or mucocutaneous candidiasis.

8. Current bacterial skin infection, secondary cellulitis, lymphangitis, or pyoderma.

9. Presence of current conditions that required systemic antimicrobial or antifungal therapy.

10. Uncontrolled diabetes mellitus, peripheral vascular disease, chronic venous stasis, or other significant condition that may have placed the subject at risk.

11. Current severe onychomycosis.

12. Any clinically significant condition or situation, other than the condition being studied, that in the opinion of the investigator would have interfered with the study evaluations or optimal participation in the study.

13. Use of any investigational drugs or device within 30 days of signing the ICF.

14. Current participation in any other clinical study.

15. Consumed excessive amounts of alcohol, abused drugs, or had any condition that would have compromised compliance with this protocol.

16. Previous participation in this study.

17. Subjects with a past history of tinea pedis infections with a lack of response to antifungal therapy (i.e., recurrent tinea pedis, more than 3 infections in the past 12 months that were unresponsive to previous antifungal therapy).

18. Subjects who, in the opinion of the investigator, would have been non-compliant with the requirements of the study protocol.

19. Employees or direct relatives of an employee of the study center or investigator.

Reviewer's Comments:

The sponsor has added additional exclusion criteria to the drug product draft guidance. The sponsor's exclusion criteria are acceptable.

Criteria for removal from the study:

A subject could discontinue the study at any time for any reason.

Subjects were to be discontinued from the study if their safety and well-being were determined to be at risk. Discontinuation was at the discretion of the investigator or at the subject's request. Discontinuation was permanent; after a subject was discontinued, he/she was not allowed to enroll again.

A subject could be discontinued from the study for any of the following reasons:

- Negative baseline culture (the subject was not required to return for an early discontinuation visit).

- The subject withdrew his or her consent for any reason.

- The subject's condition worsened and required alternative or supplemental therapy for interdigital tinea pedis during the study. The subject was to be provided with effective treatment after he or she was discontinued and that was to be documented in the source document.

- A lack of treatment response. (Subjects who were discontinued due to lack of treatment response after completing at least 7 days of treatment were considered treatment failures.)

- The subject's study medication was unblinded.

- An adverse event (AE) occurred for which the subject desired to discontinue treatment or the investigator determined that it was in the subject's best interest to discontinue study treatment.

- There was a significant protocol violation.

- The subject was non-compliant with study medication applications.
- A concomitant therapy was reported or required that was liable to interfere with the results of the study.
- The subject was lost to follow-up. The investigator documented efforts to attempt to reach the subject at least twice by telephone and by a certified follow-up letter before considering the subject lost to follow-up.
- The subject became pregnant.

Reviewer's Comments:

The sponsor's criteria for patient removal from the study are acceptable.

Prior and Concomitant Therapy:

All prior medications taken within 30 days prior to signing the informed consent form (ICF) and all concomitant therapy taken by the subject during the study were recorded on the case report form (CRF). The identity of the therapy, dose, frequency, route of administration, start and stop dates (or "continuing"), and indication were recorded.

The medications prohibited prior to Visit 1/Day 1 are listed in Table 3 with the subject exclusion criteria. In addition, the following treatments were prohibited during the study after Visit 1/Day 1.

Table 4: Medications (Prescription and Over-the-Counter) Prohibited During the Study

Antipruritics, including antihistamines, within 24 hours of study visits (Visits 2 and 3).
Topical corticosteroid, antibiotic, or antifungal therapy applied to the feet
Systemic (e.g., oral or injectable) corticosteroid, antibiotic, or antifungal therapy
Immunosuppressive medication or radiation therapy
Any other topical products applied to the feet

Medications necessary for the health and well-being of the subject were permitted if they had been at a stable dose within 30 days prior to signing the ICF. The use of any medication that could affect the course of tinea pedis was prohibited during the entire study period.

Treatments:

Study No. BTNF 1104			
Product	**Test**	**Reference**	**Vehicle**
Treatment ID	Treatment A	Treatment B	Treatment C
Product Name	Butenafine HCl Cream, 1%	Lotrimin Ultra®	Cream Vehicle of Test product
Manufacturer	Taro Pharmaceuticals Inc.	Schering-Plough HealthCare Products, Inc.	Taro Pharmaceuticals Inc.
Batch/Lot No.	S229-60052	1H02DA	S229-60051
Manufacture Date	July 04, 2011	N/A	June 30, 2011
Expiration Date	N/A	July 2014	N/A
Strength	1%	1%	N/A
Dosage Form	Cream	Cream	Cream
Bio-batch Size	160 kg	N/A	160 kg
Dose and Treatment Period	1 application BID for 7 days	1 application BID for 7 days	1 application BID for 7 days
Route of Administration	Topical	Topical	Topical

Each subject was instructed to apply the first dose at the study site. The proper use of the study medication was demonstrated and observed by study staff who were not involved in performing any clinical assessments at the study site to ensure that subjects understood the instructions. Subjects were instructed to apply a thin layer of study medication to cover the affected and immediately surrounding areas on one or both feet 2 times per day, morning and evening, for 7 consecutive days whether or not the area(s) appeared clinically healed (a total of 14 consecutive applications). Subjects were instructed not to dose within 4 hours of a scheduled study visit.

Reviewer's Comments:

- *Instructions from the product draft guidance: Wash the affected skin with soap and water and dry completely before applying study drug.*
- *Although not in the study report, the sponsor's protocol mentions the washing and drying of the affected skin prior to application of the study drug.*
- *Acceptable*

Compliance:

Compliance was determined from the diary card, on which the subject was instructed to record all applications made or missed. The number of applications was totaled by the study coordinator or designee and recorded on the CRF. Subjects who applied less than 75% or more than 125% of the 14 planned applications of study medication (less than 11 or more than 17 applications) were considered non-compliant.

Reviewer's Comments:

The sponsor's criteria for compliance are consistent with the drug product draft guidance.

Randomization:

Each eligible subject was randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups: Test, Reference, or Vehicle, respectively. Randomization was performed according to a computer-generated randomization scheme that was generated and maintained by a third party (b) (4) (b) (4)

Reviewer's Comments:

The sponsor's randomization scheme is acceptable.

Blinding:

A double-blind technique was used. The Test, Reference, and Vehicle products were identical in appearance and were packaged identically to maintain the treatment blind. Neither the subject nor the investigational staff (investigator, evaluators, sponsor, and sponsor representatives) knew which treatment a subject was receiving.

Each tube was labeled with a blank diaper label to blind the tube. A single panel label on each tube displayed the following text: protocol number, subject number, amount, instructions for use and storage, the Sponsor's name, and warnings: "For Topical Dermatologic Use Only," "Not for Ophthalmic, Oral or Intravaginal Use," and "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

The tube carton label displayed the following information: protocol number, subject number and initials, amount, date dispensed, instructions for use and storage, the Sponsor's name, and warning: "For Topical Dermatologic Use Only," and "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

Unblinding Treatment for a Subject During the Study, per Sponsor protocol:

Unblinding by the Investigator should occur only in the event of an AE or SAE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject and only with prior authorization from the Sponsor or designee. If unblinding is necessary, the Investigator or study staff should contact the Medical Monitor immediately to ensure that appropriate procedures are followed. The tear-off section of the 2-panel label contains the product identification information under the tamper-evident occluding layer. If the Investigator must identify the treatment assignment of an individual subject, the double-blind occluding layer can be removed to reveal the subject's treatment. If unblinding occurs, the subject must be discontinued from the study.

Reviewer's Comments:

The sponsor's blinding is acceptable.

2.4.3.1.2 Endpoints/Variables

Efficacy Measures

KOH
After the feet were carefully cleaned with an alcohol wipe, a KOH wet mount of target lesion skin scrapings was prepared by dissolving a portion of the scrapings in KOH solution and then examining the KOH wet mount for presence of fungal hyphae. Segmented fungal hyphae must have been identified under microscopic examination by the investigator at Visit 1/Day 1 for the subject to have entered the study.

Fungal Culture
For subjects with positive KOH at Visit 1/Day 1, skin scrapings were obtained from the same target lesion for fungal culture. A sufficient amount of scrapings were collected to facilitate fungal culture plate inoculation and were sent to the designated reference laboratory. Testing was performed to identify the isolates at the species level (e.g., *T. rubrum, T. mentagrophytes, T. tonsurans, or E. floccosum*). A positive skin fungal culture at Visit 1/Day 1 was not an inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results.

Clinical Assessments
Assessment of clinical signs and symptoms of the target lesion was performed at each visit. Scoring was based solely on the target lesion. The clinical signs (erythema, scaling, maceration, and fissuring/cracking) were graded at each visit by the same investigator if possible. Symptoms (pruritus and burning/stinging) were graded at each visit by the subject. A minimum total signs and symptoms score of 4 (with scores of at least 2 for erythema and at least 2 for scaling or pruritus at Visit 1/Day 1) was required for study entry. Prior to Protocol Amendment 2, the total signs and symptoms score was required to be at least 6 and to include a minimum score of 2 for erythema and a minimum score of 2 for scaling.

The signs and symptoms were defined as follows:

Sign/Symptom	Description
Erythema	Redness
Scaling	Thin, dry epidermal sheets shedding from skin
Maceration	Soft, moist broken-down skin
Fissuring/Cracking	Deep furrowing clefts or slits in the skin
Pruritus	Itching as determined by the subject
Burning/Stinging	Burning, stinging or tingling sensation as determined by the subject

The scale for scoring severity of signs and symptoms was as follows:

Score	Assessment	Description
0	None	Complete absence of sign or symptom
1	Mild	Slight
2	Moderate	Definitely present
3	Severe	Marked, intense

Reviewer's Comments:

- *The sponsor's procedure includes cleaning the feet with an alcohol wipe prior to the KOH wet mount, which is not included in the product draft guidance. This is acceptable.*
- *The sponsor's procedure for the fungal culture and clinical assessments are consistent with the product draft guidance.*
- *The sponsor's scale for scoring severity of signs and symptoms is consistent with the product draft guidance.*
- *Acceptable*

Safety Measures

Subjects were monitored for the occurrence of AEs, including SAEs, immediately after treatment initiation to the subject's last visit. All AEs were recorded on the CRF regardless of relationship of treatment. The investigator assessed each AE in terms of the frequency, severity, and relationship to study medication. Date of onset, action taken with the study drug, action taken with the subject, and outcome were also recorded. Any AE potentially related (defined as possibly, probably, or definitely related) to study medication was to be followed to resolution, stabilization, being deemed clinically insignificant, or until the subject was lost-to-follow-up. Subjects were queried regarding AEs at all site visits. Subjects were questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The presence or absence of specific AEs was not elicited from subjects.

Reviewer's Comments:

The sponsor's safety measures are acceptable.

Primary Endpoint:

The primary efficacy endpoint was the proportion of subjects in each treatment group who obtained therapeutic cure at Visit 3/Day 42 (± 4 days). Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2 with no individual severity score greater than 1 on the 4-point scale).

Reviewer's Comments:

The sponsor's primary endpoint is consistent with the drug product draft guidance.

2.4.3.1.3 Statistical analysis plan

The statistical analysis plan (SAP) used for the sponsor's analyses is provided in Appendix 16.1.9 of the sponsor's study report.

Patient Populations:

The sponsor performed efficacy analyses on the mITT and PP populations. The sponsor performed safety analyses on the ITT population.

Subjects who are discontinued early due to lack of treatment response after completing at least 7 days of treatment were analyzed in the mITT and PP populations as treatment failures if they met all other criteria for the corresponding populations. Subjects who applied topical drug therapy other than the study medication to the feet for treatment of irritation or pruritus after the treatment phase of the study were analyzed in the mITT and PP populations as treatment failures if they met all other criteria for the corresponding populations.

Subjects discontinued early for other reasons were excluded from the PP population but included in the mITT population using the last-observation-carried-forward (LOCF) approach if they completed at least 1 post-baseline visit.

Intent-to-Treat (ITT) Population

The sponsor's definition:
An intent-to-treat (ITT) subject was any individual who:

1. was enrolled into the study
2. applied at least 1 dose of assigned study medication.

Reviewer's Comments:

- *According to the product draft guidance, the safety population includes all randomized subjects who received study product.*
- *The sponsor's definition of the ITT (safety) population is slightly different than that of the product draft guidance, but acceptable.*

Per-Protocol (PP) Population

The sponsor's definition:
A per-protocol (PP) subject, consistent with the protocol, was any individual who:

1. was enrolled in the study and met all inclusion/exclusion criteria
2. had a positive baseline skin fungal culture for *T. rubrum, T. mentagrophytes, T. tonsurans, or E. floccosum*
3. did not take any concomitant medications prohibited by the protocol or have any other significant protocol violations
4. returned for Visit 3/Day 42 (± 4 days) within the designated visit window with a compliance rate between 75% and 125% (at least 11 applications and no more than 17 applications).

For the purpose of determining the PP status of the subject, a "protocol violation" was any subject or investigator activity that could have interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

Reviewer's Comments:

The sponsor's definition of the PP is consistent with Drug Product draft guidance.

Modified Intent-to-Treat (mITT) Population

The sponsor's definition:
A modified intent-to-treat (mITT) subject was any individual who:

1. was enrolled in the study and met all inclusion/exclusion criteria
2. had a positive baseline skin fungal culture for *T. rubrum, T. mentagrophytes, T. tonsurans, or E. floccosum*
3. applied at least 1 dose of assigned study medication
4. returned for at least 1 visit after Visit 1/Day 1.

Reviewer's Comments:

The sponsor's definition of the mITT population is consistent with the product draft guidance.

Primary Endpoint Analysis:

The sponsor's primary efficacy endpoint was the proportion of subjects in each treatment group who obtained therapeutic cure at Visit 3/Day 42 (± 4 days). Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2 with no individual severity score greater than 1 on the 4-point scale).

The Test product would be considered bioequivalent to the Reference product if the 90% confidence interval (CI) on the difference in their proportions of cures, calculated by the Wald's method with Yates' continuity correction, was contained within the limits -0.20 to +0.20 for the PP population.

The sponsor compared the difference between each active treatment (Test and Reference) group in the proportion of patients with success at Visit 3 (End of Study) with that of the vehicle group using independent, 2-sided, $\alpha = 0.05$, continuity-corrected Z-tests. The active treatment was considered superior to the Placebo if the proportion of patients with success in the active treatment group was significantly greater and statistically different than for patients in the vehicle group.

Reviewer's Comments:

The bioequivalence analysis is consistent with Drug Product draft guidance.

For determining adequate study sensitivity, the mITT study population and the LOCF should be used. The sponsor's analysis for study sensitivity is acceptable.

Missing values or Dropouts:

Missing efficacy data were imputed using the LOCF method in the mITT analysis. In the PP analysis, efficacy data from the subject's last visit were carried forward to all the subsequent visits only for subjects who discontinued early due to lack of treatment response.

Subjects who were discontinued early due to lack of treatment effect after completing at least 7 days of treatment and subjects who applied topical drug therapy other than the study medication to the feet for treatment of irritation or pruritus after the treatment phase of the study were considered as treatment failures in the analysis of the primary endpoint for the mITT and PP populations if they met the criteria for the corresponding populations.

For demographic and baseline characteristics and the safety profile, each variable was analyzed using all available data. Subjects with missing data were excluded only from the analyses for which data were not available.

Reviewer's Comments:

The sponsor's statistical plan for missing values and dropouts is acceptable.

Changes to the Planned Analyses

Although the secondary efficacy endpoints were deleted by Protocol Amendment 3, those analyses were described in the Statistical Analysis Plan and are therefore presented briefly in this report. Although the protocol identified MedDRA version 14.0, version 14.1 was used for coding in this study.

Reviewer's Comments:

There are no secondary efficacy endpoints in the product draft guidance. Changing the MedDRA version from 14.0 to 14.1 had no impact on the planned analyses. The sponsor's changes to the planned analyses are acceptable.

Changes to the Conduct of the Study

Subjects were first enrolled in the study under Protocol Version 2 (Amendment 1, 19 December 2011). Protocol Version 4 (Amendment 3, 10 April 2012), the final version, and summaries of the changes in Amendment 2 and Amendment 3 are provided in Appendix 16.1.1 Final Protocol, Version 4 (Amendment 3, 10 April 2012).

The major changes in Amendment 2 were based on recommendations from the FDA:

- Inclusion criterion #5 was changed from requiring the sum of clinical signs and symptoms scores of the target lesion of at least 6 to at least 4 and the minimum score of 2 for scaling was changed to a minimum score of 2 for scaling or pruritus.
- *T. tonsurans* was added as an allowed causative dermatophyte.
- The PP definition was revised to delete the wording indicated here by strikethrough font: "…(d) returned for ~~Visit 2/Day 8 (+3 days) and~~ Visit 3/Day 42 (±4 days), within the designated visit window with a compliance rate between 75% and 125% (at least 11 applications and no more than 17 applications) ~~OR discontinued the study due to lack of treatment effect after at least 7 consecutive applications~~."

- The definition of treatment failure was changed from lack of treatment response after completing at least 7 consecutive applications to after completing at least 7 days of treatment.

The major changes in Amendment 3 were based on the FDA BE Draft Guidance for Butenafine Hydrochloride (March 2012):

- Inclusion criterion #2 was changed from requiring subjects to be at least 12 years of age to at least 18 years of age and references to assent were deleted.
- The secondary efficacy endpoints (proportion of subjects with clinical cure at Visit 3 and with mycological cure at Visit 3) were deleted.

Reviewer's Comments:

The study and associated data are typically evaluated with respect to the product draft guidance. The clinical review of this study data has taken into consideration the sponsor's more stringent criteria in the screening out of the study patients.

Safety Analysis

2.4.3.2 Study Conduct

Patient Disposition:

Table 5: Patient Disposition (per Sponsor)

	Number (%) of Subjects			
	Test	Reference	Vehicle	Overall
Number Randomized	283	283	141	707
Number Completed study	213 (75.3%)	212 (74.9%)	105 (74.5%)	530 (75.0%)
Total Discontinued	70 (24.7%)	71 (25.1%)	36 (25.5%)	177 (25.0%)
Reason Discontinued				
- Negative baseline culture	62 (21.9%)	54 (19.1%)	27 (19.1%)	143 (20.2%)
- Subject decision/withdrawal of consent	2 (0.7%)	5 (1.8%)	2 (1.4%)	9 (1.3%)
- Adverse event, including intercurrent illness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Subject's condition worsens and requires alternative or supplemental therapy for interdigital tinea pedis during the study	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Lack of treatment response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Subject's medication is unblinded	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
- Protocol violation	0 (0.0%)	0 (0.0%)	2 (1.4%)	2 (0.3%)
- Subject is non-compliant with study medication applications	2 (0.7%)	3 (1.1%)	2 (1.4%)	7 (1.0%)
- Concomitant therapy is reported or required that is liable to interfere with the results of the study	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Lost to follow-up	4 (1.4%)	8 (2.8%)	3 (2.1%)	15 (2.1%)
- Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.1.1.2

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Protocol Violations:

Table 6: Major Protocol Deviations/Violations (per Sponsor)

	Number (%) of Subjects			
	Test (N=283)	Reference (N=283)	Vehicle (N=141)	Overall (N=707)
Negative culture at baseline	80 (28.3%)	65 (23.0%)	33 (23.4%)	178 (25.2%)
Inclusion/exclusion criteria violation	2 (0.7%)	3 (1.1%)	2 (1.4%)	7 (1.0%)
No post-baseline visit	1 (0.4%)	6 (2.1%)	3 (2.1%)	10 (1.4%)
Compliance rate not met*	1 (0.4%)	3 (1.1%)	0 (0.0%)	4 (0.6%)
Missed Visit 3	4 (1.4%)	7 (2.5%)	1 (0.7%)	12 (1.7%)
Visit 3 out of window	11 (3.9%)	6 (2.1%)	10 (7.1%)	27 (3.8%)
Lack of data at Visit 3 to determine therapeutic response	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
Dosing Compliance	1 (0.4%)	1 (0.4%)	1 (0.7%)	3 (0.4%)
Prohibited medication	1 (0.4%)	0 (0.0%)	1 (0.7%)	2 (0.3%)
Study Compliance	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)

Major protocol deviations/violations (PDs/PVs) are those that exclude subjects from the per-protocol population.

Subjects with multiple major PDs/PVs are presented under each category as appropriate. Subjects who had negative baseline culture or no post-baseline visit are not counted under PDs/PVs related to Visit 3 or compliance.

*For qualification of the PP analysis, compliance rate is required to be 75%-125% (i.e. 11-17 applications), inclusive.

Source: Listing 16.2.1.2.1

o:\Studies\Taro\BTNF 1104\Biometrics\programs\tables\14.1.4_pv.sas ran on November 6, 2012 at 9:13 on data from 05NOV2012.

Reviewer's Comments:

- *The sponsor's data and protocol deviations were reviewed.*
- *The following changes to the Sponsor's mITT & PP populations to form the FDA mITT (FmITT) and FDA PP (FPP) populations are made:*

Table 7: Changes to the Sponsor's mITT & PP populations to form FDA mITT (FmITT) and FDA PP (FPP) populations

Recommendation/Reason/Patient#	Violation
Exclude from both FDA mITT & PP populations	
(b) (6)	
Exclude from only FDA PP population	
None	
Include in FDA PP population	
None	

Patient Populations:

Table 8: Number of Subjects in the Sponsor's and FDA's ITT, mITT and PP Populations (per Sponsor and per FDA Statistician)

	Test	Reference	Vehicle	Total
Enrollment	**283**	**283**	**141**	**707**
Total exclusion from Sponsor's ITT population	0	0	0	0
Total Sponsor's ITT population (ITT)	**283**	**283**	**141**	**707**
Total exclusion from Sponsor's PP population	100	89	49	238
Total Sponsor's PP population (PP)	**183**	**194**	**92**	**469**
Additional exclusion for FDA's PP population				
Prohibited Medication	5	1	0	6
Inclusion criteria violation (<18 years old)	1	1	3	5
Inclusion criteria violation (clinical diagnosis)	0	1	1	2
Exclusion criteria violation (past medical history)	0	0	1	1
Total FDA's PP Population (FPP)	**177**	**191**	**88**	**456**
Total exclusion from sponsor's mITT population	82	72	38	192
Total Sponsor's mITT population	**201**	**211**	**103**	**515**
Additional exclusions for FDA's mITT population				
Prohibited Medication	5	1	0	6
Inclusion criteria violation (<18 years old)	1	1	3	5
Inclusion criteria violation (clinical diagnosis)	0	1	1	2
Exclusion criteria violation (past medical history)	0	0	1	1
Total FDA's mITT population (FITT)	**195**	**208**	**99**	**502**
Number discontinued study	6	8	5	19
Number completed study	189	200	94	483

Baseline Characteristics:

Retention of Reserve Samples:

Per the sponsor's protocol:
Each investigational site where study medication is dispensed to at least 1 subject will be required to randomly select 1 block (5 consecutively numbered subject boxes) of study medication to be maintained as retain samples. The Investigator will maintain one randomly selected block of study medication from each shipment of study medication received. As per Title 21 CFR 320.38 and 320.63 and the guidance "Handling and Retention of BA [Bioavailability] and BE [Bioequivalence] Testing Samples," "Each reserve sample shall be stored under conditions consistent with the product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Retain samples shall be stored for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used."

If not maintained by the study site, a third-party storage facility will be identified where the retain sample study medication may remain until such time as notification is received from the Sponsor that the samples are no longer required.

Demographics

Table 9 lists the demographics for the ITT population. According to the sponsor's analysis, the treatment groups in the ITT population were comparable for most demographic characteristic (P > 0.05) except age (years) (p=0.017).

Table 9: Demographic Characteristics: BTNF 1104, Butenafine Hydrochloride Cream, 1% (ITT, per sponsor)

Parameter	Category	Test (N=283)	Reference (N=283)	Vehicle (N=141)	Overall (N=707)	p-value
Gender	Female	60 (21.2%)	63 (22.3%)	39 (27.7%)	162 (22.9%)	0.272[1]
	Male	223 (78.8%)	220 (77.7%)	102 (72.3%)	545 (77.1%)	
Ethnicity	Hispanic or Latino	70 (24.7%)	76 (26.9%)	34 (24.1%)	180 (25.5%)	0.672[1]
	Not Hispanic or Latino	213 (75.3%)	207 (73.1%)	107 (75.9%)	527 (74.5%)	
	Not Willing to Provide	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Race	White or Caucasian	168 (59.4%)	179 (63.3%)	83 (58.9%)	430 (60.8%)	0.764[1]
	Asian	3 (1.1%)	1 (0.4%)	1 (0.7%)	5 (0.7%)	
	Native Hawaiian or Other Pacific-Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	American Indian or Alaska Native	2 (0.7%)	3 (1.1%)	1 (0.7%)	6 (0.8%)	
	Black or African American	105 (37.1%)	98 (34.6%)	55 (39.0%)	258 (36.5%)	
	Other	2 (0.7%)	2 (0.7%)	0 (0.0%)	4 (0.6%)	
	Mixed*	3 (1.1%)	0 (0.0%)	1 (0.7%)	4 (0.6%)	
Age (years)	N	283	283	141	707	
	Mean ± SD	47.3 ± 15.17	45.3 ± 15.52	44.3 ± 15.67	45.9 ± 15.44	0.017[2]
	Median	47.0	44.0	43.0	46.0	
	Min, Max	17, 90	12, 92	15, 89	12, 92	

Source: Table 14.1.5.3, Listing 16.2.1.3.1
[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.
[2] P-value for treatment comparison from nonparametric ranked two-way analysis of variance (ANOVA) with fixed factors of treatment and site.
*Subjects who report more than one race are categorized as Mixed race.

Table 10 lists the demographics for the PP population. According to the sponsor's analysis, the treatment groups in the PP population were comparable for most demographic characteristics (P > 0.05).

Table 10: Demographic Characteristics: BTNF 1104, Butenafine Hydrochloride Cream, 1% (PP Population, per sponsor)

Parameter	Category	Test (N=183)	Reference (N=194)	Vehicle (N=92)	Overall (N=469)	p-value
Gender	Female	34 (18.6%)	47 (24.2%)	25 (27.2%)	106 (22.6%)	0.170[1]
	Male	149 (81.4%)	147 (75.8%)	67 (72.8%)	363 (77.4%)	
Ethnicity	Hispanic or Latino	52 (28.4%)	54 (27.8%)	23 (25.0%)	129 (27.5%)	0.807[1]
	Not Hispanic or Latino	131 (71.6%)	140 (72.2%)	69 (75.0%)	340 (72.5%)	
	Not Willing to Provide	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Race	White or Caucasian	118 (64.5%)	128 (66.0%)	58 (63.0%)	304 (64.8%)	0.754[1]
	Asian	2 (1.1%)	0 (0.0%)	1 (1.1%)	3 (0.6%)	
	Native Hawaiian or Other Pacific-Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	American Indian or Alaska Native	2 (1.1%)	2 (1.0%)	0 (0.0%)	4 (0.9%)	
	Black or African American	57 (31.1%)	63 (32.5%)	33 (35.9%)	153 (32.6%)	
	Other	2 (1.1%)	1 (0.5%)	0 (0.0%)	3 (0.6%)	
	Mixed*	2 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	
Age (years)	N	183	194	92	469	
	Mean ± SD	47.3 ± 15.81	46.0 ± 15.63	44.7 ± 16.89	46.3 ± 15.95	0.257[2]
	Median	47.0	45.5	42.0	46.0	
	Min, Max	17, 90	14, 92	15, 89	14, 92	

Source: Table 14.1.5.1, Listing 16.2.1.3.1
[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.
[2] P-value for treatment comparison from two-way analysis of variance (ANOVA) with fixed factors of treatment and site.
*Subjects who report more than one race are categorized as Mixed race.

No subject had a positive pregnancy test during the study.

Reviewer's Comments:

Although there was a difference for age in the ITT population (p=0.017), treatment groups were comparable for the mITT and PP population. Subjects under the age of 18 are excluded from the FDA analyses. The sponsor's PP population includes subjects under the age of 18.

Baseline Dermatological Examination:

Table 11: KOH and Mycological Evaluations of Target Site at Baseline: BTNF 1104, Butenafine Hydrochloride Cream, 1% (PP Population, per sponsor)

Parameter	Category	Test (N=183)	Reference (N=194)	Vehicle (N=92)	Overall (N=469)
KOH	N	183	194	92	469
	Positive	183 (100.0%)	194 (100.0%)	92 (100.0%)	469 (100.0%)
	Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mycological Culture	N	183	194	92	469
	Trichophyton rubrum	163 (89.1%)	171 (88.1%)	80 (87.0%)	414 (88.3%)
	Epidermophyton floccosum	6 (3.3%)	9 (4.6%)	5 (5.4%)	20 (4.3%)
	Trichophyton mentagrophytes	14 (7.7%)	14 (7.2%)	7 (7.6%)	35 (7.5%)
	Trichophyton tonsurans	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other Dermatophyte	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Subjects may be positive for more than one dermatophyte.

Table 12: KOH and Mycological Evaluations of Target Site at Baseline: BTNF 1104, Butenafine Hydrochloride Cream, 1% (mITT Population, per sponsor)

Statistics		Test (N=201)	Reference (N=211)	Vehicle (N=103)	Overall (N=515)
KOH	N	201	211	103	515
	Positive	201 (100.0%)	211 (100.0%)	103 (100.0%)	515 (100.0%)
	Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mycological Culture	N	201	211	103	515
	Trichophyton rubrum	180 (89.6%)	186 (88.2%)	90 (87.4%)	456 (88.5%)
	Epidermophyton floccosum	7 (3.5%)	10 (4.7%)	6 (5.8%)	23 (4.5%)
	Trichophyton mentagrophytes	14 (7.0%)	14 (6.6%)	7 (6.8%)	35 (6.8%)
	Trichophyton tonsurans	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Other Dermatophyte	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Subjects may have been positive for more than one dermatophyte.

Reviewer's Comments:

The baseline dermatological examination parameters appear to be similar between the test and reference products. As recommended in the product draft guidance, greater than 50% of PP and mITT populations (per sponsor) patients were positive for T. rubrum.

Table 13: Clinical Assessment of Target Site at Baseline: BTNF 1104, Butenafine Hydrochloride Cream, 1% (PP Population, per sponsor)

	Category	Test (N=183)	Reference (N=194)	Vehicle (N=92)	Overall (N=469)
Erythema	N	183	194	92	469
	None (0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mild (1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (2)	161 (88.0%)	171 (88.1%)	85 (92.4%)	417 (88.9%)
	Severe (3)	22 (12.0%)	23 (11.9%)	7 (7.6%)	52 (11.1%)
Scaling	N	183	194	92	469
	None (0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mild (1)	1 (0.5%)	4 (2.1%)	2 (2.2%)	7 (1.5%)
	Moderate (2)	127 (69.4%)	137 (70.6%)	59 (64.1%)	323 (68.9%)
	Severe (3)	55 (30.1%)	53 (27.3%)	31 (33.7%)	139 (29.6%)
Maceration	N	183	194	92	469
	None (0)	71 (38.8%)	82 (42.3%)	32 (34.8%)	185 (39.4%)
	Mild (1)	65 (35.5%)	59 (30.4%)	28 (30.4%)	152 (32.4%)
	Moderate (2)	35 (19.1%)	41 (21.1%)	26 (28.3%)	102 (21.7%)
	Severe (3)	12 (6.6%)	12 (6.2%)	6 (6.5%)	30 (6.4%)
Fissuring/Cracking	N	183	194	92	469
	None (0)	63 (34.4%)	67 (34.5%)	29 (31.5%)	159 (33.9%)
	Mild (1)	80 (43.7%)	91 (46.9%)	35 (38.0%)	206 (43.9%)
	Moderate (2)	36 (19.7%)	31 (16.0%)	25 (27.2%)	92 (19.6%)
	Severe (3)	4 (2.2%)	5 (2.6%)	3 (3.3%)	12 (2.6%)

Parameter	Category	Test (N=183)	Reference (N=194)	Vehicle (N=92)	Overall (N=469)
Pruritus (Subject's Rating)	N	183	194	92	469
	None (0)	21 (11.5%)	21 (10.8%)	7 (7.6%)	49 (10.4%)
	Mild (1)	50 (27.3%)	42 (21.6%)	23 (25.0%)	115 (24.5%)
	Moderate (2)	71 (38.8%)	91 (46.9%)	42 (45.7%)	204 (43.5%)
	Severe (3)	41 (22.4%)	40 (20.6%)	20 (21.7%)	101 (21.5%)
Burning/Stinging (Subject's Rating)	N	183	194	92	469
	None (0)	86 (47.0%)	82 (42.3%)	41 (44.6%)	209 (44.6%)
	Mild (1)	52 (28.4%)	48 (24.7%)	22 (23.9%)	122 (26.0%)
	Moderate (2)	34 (18.6%)	41 (21.1%)	21 (22.8%)	96 (20.5%)
	Severe (3)	11 (6.0%)	23 (11.9%)	8 (8.7%)	42 (9.0%)
Total Signs & Symptoms Score	N	183	194	92	469
	Mean ± SD	8.8 ± 2.50	8.9 ± 2.41	9.3 ± 2.51	9.0 ± 2.46
	Median	8.0	8.0	9.0	8.0
	Min, Max	5, 17	4, 15	5, 15	4, 17

Table 14: Clinical Assessment of Target Site at Baseline: BTNF 1104, Butenafine Hydrochloride Cream, 1% (mITT Population, per sponsor)

Statistics		Test (N=201)	Reference (N=211)	Vehicle (N=103)	Overall (N=515)
Erythema	N	201	211	103	515
	None (0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mild (1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (2)	175 (87.1%)	187 (88.6%)	94 (91.3%)	456 (88.5%)
	Severe (3)	26 (12.9%)	24 (11.4%)	9 (8.7%)	59 (11.5%)
Scaling	N	201	211	103	515
	None (0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mild (1)	1 (0.5%)	5 (2.4%)	2 (1.9%)	8 (1.6%)
	Moderate (2)	137 (68.2%)	145 (68.7%)	65 (63.1%)	347 (67.4%)
	Severe (3)	63 (31.3%)	61 (28.9%)	36 (35.0%)	160 (31.1%)
Maceration	N	201	211	103	515
	None (0)	77 (38.3%)	92 (43.6%)	38 (36.9%)	207 (40.2%)
	Mild (1)	69 (34.3%)	63 (29.9%)	29 (28.2%)	161 (31.3%)
	Moderate (2)	41 (20.4%)	44 (20.9%)	28 (27.2%)	113 (21.9%)
	Severe (3)	14 (7.0%)	12 (5.7%)	8 (7.8%)	34 (6.6%)
Fissuring/Cracking	N	201	211	103	515
	None (0)	73 (36.3%)	74 (35.1%)	37 (35.9%)	184 (35.7%)
	Mild (1)	84 (41.8%)	98 (46.4%)	37 (35.9%)	219 (42.5%)
	Moderate (2)	40 (19.9%)	34 (16.1%)	25 (24.3%)	99 (19.2%)
	Severe (3)	4 (2.0%)	5 (2.4%)	4 (3.9%)	13 (2.5%)
Pruritus (Subject's Rating)	N	201	211	103	515
	None (0)	25 (12.4%)	22 (10.4%)	9 (8.7%)	56 (10.9%)
	Mild (1)	53 (26.4%)	45 (21.3%)	24 (23.3%)	122 (23.7%)
	Moderate (2)	74 (36.8%)	101 (47.9%)	47 (45.6%)	222 (43.1%)
	Severe (3)	49 (24.4%)	43 (20.4%)	23 (22.3%)	115 (22.3%)
Burning/Stinging (Subject's Rating)	N	201	211	103	515
	None (0)	95 (47.3%)	91 (43.1%)	46 (44.7%)	232 (45.0%)
	Mild (1)	57 (28.4%)	52 (24.6%)	24 (23.3%)	133 (25.8%)
	Moderate (2)	37 (18.4%)	45 (21.3%)	24 (23.3%)	106 (20.6%)
	Severe (3)	12 (6.0%)	23 (10.9%)	9 (8.7%)	44 (8.5%)

Statistics		Test (N=201)	Reference (N=211)	Vehicle (N=103)	Overall (N=515)
Total Signs & Symptoms Score	N	201	211	103	515
	Mean ± SD	8.8 ± 2.50	8.9 ± 2.37	9.2 ± 2.50	8.9 ± 2.45
	Median	8.0	8.0	9.0	8.0
	Min, Max	4, 17	4, 15	5, 15	4, 17

2.4.3.3 Results

2.4.3.3.1 Primary Endpoint

The primary efficacy endpoint was the proportion of subjects in each treatment group who obtained therapeutic cure at Visit 3/Day 42 (± 4 days). Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2 with no individual severity score greater than 1 on the 4-point scale).

The sponsor's and FDA's statistical analysis, in the PP population, shows the 90% CI of the difference in therapeutic cure rates between the test product and RLD treatment groups at the

test-of-cure visit (study Day 38-46) was (-0.61%, 17.52%), within [-0.20, +0.20] for dichotomous variables (success versus failure) for both analyses. The test product and RLD are comparable.

According to the sponsor's and FDA's analysis, the two active treatments were statistically superior to placebo ($p<0.05$) with regard to the therapeutic cure rate at the test-of-cure visit (study Day 38-46), using the mITT study population and Last Observation Carried Forward (LOCF).

Table 15: Primary Endpoint Analysis: Proportion of Subjects with Therapeutic Cure at Visit 3/Day 42 (± 4 days) (per sponsor and FDA Statistician)

	Sponsor			FDA		
	Test	**Reference**	**Placebo**	**Test**	**Reference**	**Placebo**
PP Population						
N	183	194	92	177	191	88
Cure	106 (57.9%)	96 (49.5%)	14 (15.2%)	103 (58.19%)	95 (49.74%)	13 (14.77%)
90% CI for Test and Reference	(-0.51%, 17.39%)[1]			(-0.61, 17.52)		

* From ANDA 205181 in EDR[0000 (1) 02/04/2013 ORIG-1/Multiple Categories/Subcategories/ module 5.3.5.1/Study Report Body/report-body/page 64/92 Table 14.2.1]

mITT = modified intent-to-treat; N = number of patients; PP = per-protocol; vs = versus

The last-observation-carried-forward approach was used to impute missing efficacy results for the mITT and PP patients who discontinued due to treatment failure.

Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2 with no individual severity score greater than 1 on the 4-point scale).

[1]The sponsor's confidence intervals for the proportional difference were calculated using Wald's method with Yates' continuity correction.

[2]The sponsor's p values for comparing proportions used a Z-test with continuity correction.

Table 16: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the sponsor's mITT Population and FDA's mITT Population

	Sponsor			P-value for Superiority		FDA			P-value for Superiority	
	Test	Reference	Placebo	Test vs Vehicle	Reference vs. Vehicle	Test	Reference	Placebo	Test vs Vehicle	Reference vs. Vehicle
N	201	211	103			195	208	99		
Cure	112(55.7%)	102(48.3%)	15(14.6%)	<.0001◊		109(55.90%)	101(48.56%)	14(14.14%)	<.0001*	
No Cure	89(44.3%)	109(51.7%)	88(85.4%)		<.001◊	86(44.10%)	107(51.44%)	85(85.86%)		<.0001*

◊P-values for treatment comparisons from two-sided Z-tests with continuity correction
*results from both Fisher's exact and approximate Z tests

2.4.4 Bioequivalence Conclusion

The FDA's statistical analysis shows the 90% CI of the difference in therapeutic cure rates between the test product and RLD treatment groups at the test-of-cure visit (study Day 38-46) was (-0.61%, 17.52%), within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population for Study BTNF 1104 (1% strength).

The test product and RLD were statistically superior to placebo ($p<0.05$) with regard to the therapeutic cure rate at the test-of-cure visit (study Day 38-46), using the mITT study population and Last Observation Carried Forward (LOCF).

2.5 Comparative Review of Safety

2.5.1 Brief Statement of Conclusions

These studies showed similar TEAEs with use of the test and reference products in both studies for ITT patients. A brief summary is provided below.

Study #	Total (N)	Test (n)	RLD (n)	Placebo (n)	Comment
Study BTNF 1104 (1% strength)	707	283	283	141	
Patients with at least one TEAE	36 (5.1%)	12 (4.2%)	16 (5.7%)	8 (5.7%)	• 2 SAEs were reported (RLD)
Discontinued study drug due to above AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Subjects with at least 1 Mild TEAEs	21 (3.0%)	8 (2.8%)	8 (2.8%)	5 (3.5%)	
Subjects with at least 1 Moderate TEAEs	13 (1.8%)	4 (1.4%)	6 (2.1%)	3 (2.1%)	
Subjects with at least 1 Severe TEAEs	2 (0.3%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	
TEAEs considered to be possibly, probably, or definitely related to study medication	4 (0.6%)	1 (0.4%)	3 (1.1%)	0 (0.0%)	
Application Site Reaction	1 (0.1%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	

2.5.2 Description of Adverse Events

Of the 707 ITT treated subjects, 36 experienced 1 or more TEAEs during the study (4.2% Test, 5.7% Reference, 5.7% Vehicle). No TEAE occurred in more than 1.4% of subjects in any treatment group. The most frequently reported TEAEs were upper respiratory tract infection and headache, which were reported for 4 and 3 subjects overall, respectively. Subjects with at least 1 Mild TEAEs for test, reference, and vehicle groups were 2.8%, 2.8%, and 3.5%, respectively. Subjects with at least 1 Moderate TEAEs for test, reference, and vehicle groups were 1.4%, 2.1%, and 2.1%, respectively. Among the 36 subjects with TEAEs, subjects with at least 1 severe event were reported for 2 subjects (0.7%) in the Reference group and no subjects in the Test and Vehicle groups. TEAEs considered to be possibly, probably, or definitely related to study medication were reported for 1 subject (0.4%) in the Test group, 3 subjects (1.1%) in the Reference group, and no subjects in the Vehicle group. There was 1 report of a MedDRA System Organ Class skin and subcutaneous tissue disorder TEAE (pruritus, Reference group). Two subjects, both in the Reference group, had SAEs (car accident and pneumonia) that were considered unlikely related to study medication. No deaths were reported and no subject was discontinued from the study or had treatment interrupted due to TEAEs.

Reviewer's Comment:

The sponsor's analysis results indicate there was no statistically significant difference between the test and reference products in the % of subjects reporting:

- *TEAEs regardless of the relationship to the study medication for the ITT population. (p-value = 0.562.)*
- *TEAEs possibly, probably, or definitely related to study medication for the ITT population. (p-value = 0.624)*

The sponsor provided data on TEAEs by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Subjects. These data were further divided into the following categories:

- *Severity (mild, moderate, severe)*
- *Relationship to Study Medication (unrelated, related)*

The sponsor did not provide inferential statistics on the TEAEs data.

Table 17: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs) for Intent-to-Treat Subjects (per sponsor)

Relationship to Study Medication	Test (N=283)	Reference (N=283)	Vehicle (N=141)	p-value Test vs. Reference
Subjects with Treatment-Emergent Adverse Events (TEAEs) Regardless Relationship to Study Medication	12 (4.2%)	16 (5.7%)	8 (5.7%)	0.562[1]
Subjects with Treatment-Emergent Adverse Events (TEAEs) Possibly, Probably, or Definitely Related to Study Medication	1 (0.4%)	3 (1.1%)	0 (0.0%)	0.624[1]

[1] P-values for comparisons between the two active treatment groups from Fisher's exact tests.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Review of the OSI Report

An OSI inspection was requested on 09/04/2013.[3]
At the time of this review, the inspection results are pending.

2.6.2 Review of the FDA Statistical Report

The FDA statistical analyses support the bioequivalence of the Test and the Reference products. The FDA's statistical analysis shows the 90% CI of the difference in therapeutic cure rates between the test product and RLD treatment groups at the test-of-cure visit (study Day 38-46) was (-0.61%, 17.52%), within the established bioequivalence limits of [-0.20, +0.20].

The proportion of patients with therapeutic cure for the Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo.

For details of the FDA statistical analyses, please see Section 2.4.3.3 of this review.

[3] DARRTS ANDA 205181 09/04/2013 FRM-CONSULT-09(Biopharmaceutical Inspections Request) Original-1 (Unknown)

2.7 Formulation

Table 18: Test Product Formulation[4]

Strength (Label claim)	1%			
Ingredient	**Quality Standard**	**Quantity (% w/w)**	**mg/g**	**Function**
Butenafine Hydrochloride	Taro	1.000	10.00	Active Pharmaceutical Ingredient
White Petrolatum	USP	(b) (4)		
Cetyl Alcohol	NF			
Stearic Acid	NF			
Glyceryl Monostearate SE	Taro			
Propylene Glycol Dicaprylate	Taro			
Purified Water	USP			
Glycerin	USP			
Polyoxyethylene (23) Cetyl Ether	Taro			
Trolamine	NF			
Sodium Benzoate	NF			
Benzyl Alcohol	NF			
Total theoretical weight	--	100.00	1000.0	---

Table 19: RLD Formulation[5]

Ingredients	**Percentage (w/w)**
Purified water USP	(b) (4)
Propylene glycol dicaprylate	
Glycerine USP	
Cetyl alcohol NF	
Glyceryl monostearate	
White petrolatum USP	
Stearic acid NF	
Polyoxyethylene cetyl ether	
Butenafine HCl	
Benzyl alcohol NF	
Diethanolamine NF	
Sodium benzoate NF	

[4] \\cdsesub1\evsprod\anda205181\0000\m3\32-body-data\32p-drug-prod\butenafine-hydrochloride-cream-topical-cream-taro-canada\32p1-desc-comp\descr-comp-dp.pdf, page 2/2

[5] DARRTS NDA 021307 10/04/2005 FRM-ADMIN-42(Action Package) Original-1 (Type 8- Partial Rx to OTC Switch), page 343/506

Table 20: Formulation Comparison

Inactive Ingredient	Test (%w/w)	RLD (%w/w)
White petrolatum	(b) (4)	
Cetyl alcohol		
Stearic acid		
Glyceryl monostearate		
Propylene glycol dicaprylate		
Purified water		
Glycerin		
Polyoxyethylene cetyl ether		
Trolamine		
Sodium benzoate		
Benzyl alcohol		
Diethanolamine		

Reviewer's Comment:

The test and reference products are quantitatively and qualitatively different. These qualitative and quantitative differences are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Regulatory Support Branch.

(b) (4)

The study results show no apparent effect of the formulation differences on product performance or safety. The test product formulation is acceptable.

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The sponsor's and FDA's statistical analysis, in the PP population, shows the 90% CI of the difference in therapeutic cure rates between the test product and RLD treatment groups at the test-of-cure visit (study Day 38-46) was (-0.61%, 17.52%), within [-0.20, +0.20] for dichotomous variables (success versus failure) for both analyses. The test product and RLD are comparable.

According to the sponsor's and FDA's analysis, the two active treatments were statistically superior to placebo ($p<0.05$) with regard to the therapeutic cure rate at the test-of-cure visit.

2.8.2 Recommendations

From a clinical bioequivalence standpoint, this application is recommended for approval, pending satisfactory OSI inspection.

OFFICE OF GENERIC DRUGS CLINICAL REVIEW

CLINICAL BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 205181 APPLICANT: Taro Pharmaceuticals U.S.A., Inc.

DRUG PRODUCT: Butenafine Hydrochloride Cream, 1%

The Division of Clinical Review has completed its review **based on the information available prior to the Office of Scientific Investigation (OSI) inspection findings** and has no further questions at this time.

Based on information available prior to OSI inspection findings, the data submitted to ANDA 205181, using the primary endpoint of the proportion of subjects in each treatment group who obtained therapeutic cure at Visit 3/Day 42 (± 4 days) are adequate to demonstrate bioequivalence of Taro Pharmaceuticals U.S.A., Inc.'s Butenafine Hydrochloride Cream, 1% with the reference listed drug Lotrimin Ultra® (Butenafine Hydrochloride Cream), 1%. Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2 with no individual severity score greater than 1 on the 4-point scale).

Please note that the clinical bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

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

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

/s/

SUNNY Y TSE
06/24/2014

SARAH H Seung
06/24/2014

JOHN R PETERS
06/24/2014

DALE P CONNER
06/25/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

STATISTICAL REVIEW(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA #:	205181
Drug Name:	Generic version of Butenafine Hydrochloride Cream, 1%
Indication(s):	Athlete's foot
Reference Listed Drug:	Lotrimin Ultra® Cream 1% (MSD Consumer Care Inc.)
Applicant:	Taro Pharmaceuticals USA Inc.,
Date(s):	Submitted February 4, 2013
Biometrics Division:	Division of Biometric VI
Statistical Reviewer:	Yu-te Wu, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D., Team Leader
Medical Division:	Division of Clinical Review
Clinical Team:	Sunny Tse, Pharm D., Sarah Seung, Pharm D.
Keywords:	Bioequivalence, superiority, athlete's foot

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1 EXECUTIVE SUMMARY

The data from one clinical study in ANDA 205181 support the conclusion that Taro Pharmaceuticals USA Inc Butenafine HCI Cream 1% (test product) is clinically equivalent to Lotrimin Ultra® Butenafine HCI Cream, 1% (reference product) in the treatment of interdigital tinea pedis.

The purpose of this review is to assess the safety and bioequivalence of a generic Butenafine HCI Cream 1% and reference listed Lotrimin Ultra® (Butenafine HCI Cream, 1%), and to compare both active treatments to a vehicle control in the treatment of interdigital tinea pedis. Study BTNF104 is the only clinical study that the sponsor submitted to support this application. It was a double-blind, randomized, parallel-group, vehicle-controlled and multicenter study conducted in the US. Seven hundred seven subjects were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: test, reference or vehicle, respectively. The primary efficacy endpoint is the proportion of subjects in each treatment group who achieved therapeutic cure at Visit3/Day 42(±4 days). Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2 with no individual severity score greater than 1 on the 4-point scale). No secondary efficacy endpoint was specified in this study. The primary analysis population for bioequivalence testing was the FDA's per-protocol population,and the FDA's modified ITT population for the superiority testing.

There was no major statistical or data quality issue in this application. The findings from reviewer's analyses were consistent with sponsor's analyses. The test product (58.2%) was bioequivalent to the reference product (49.7%) in the FDA's PP population with the 90% CI on the difference between two rates being (-0.61%, 17.52%). This is within the range of -20% to +20%, demonstrating equivalence. The test (55.9%) and reference (48.56%) products were both superior over vehicle (14.14%) in the FDA's mITT population with $p<0.0001$.

2 INTRODUCTION

2.1 Overview

The applicant has developed Butenafine Hydrochloride Cream, 1%; and seeks to show bioequivalence of this generic version to Lotrimin Ultra® (Butenafine HCl Cream, 1%). Lotrimin Ultra® is indicated for the topical treatment of athlete's foot between the toes, jock itch, and ringworm. . Butenafine HCl Cream 1% is a benzylamine derivative with a similar mode of action as the allylamine class of antifungal drugs. Butenafine HCl has shown to be active against most strains of the following microorganisms both in vitro and in clinical infections: *E. floccosum, Malassezia furfur, T. mentagrophytes, T. Rubrum, and T. tonsurans.*

Study BTNF 1104 was a double-blind, randomized, parallel-group, vehicle-controlled and multicenter study to evaluate the safety and bioequivalence of a generic Butenafine HCl Cream 1% and reference listed Lotrimin Ultra® (Butenafine HCl Cream, 1%), and to compare both active treatments to a vehicle control in the treatment of interdigital tinea pedis.

Reference drug

Reference Listed Drug	Lotrimin Ultra® Cream, 1%
RLD Firm	MSD Consumer Care Inc.
NDA #	21-307
Date of RLD Approval	December 7, 2001
Approved Indication(s)	For the topical treatment of interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. Floccosum, T. Mentagrophytes, T. rubrum, and T. tonsurans.*
Recommended Dosing Regimens	For interdigital tinea pedis, the cream should be applied twice daily for 1 week (morning and night) or once daily for 4 weeks, or as directed by a doctor. For tinea corporis and tinea cruris, it should be applied once daily for 2 weeks, or as directed by a doctor.

Study BTNF104 is the only clinical study that the sponsor submitted to support this application. Subjects were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: test, reference or vehicle, respectively. The study enrolled subjects from 20 sites in the US. Protocols were amended three times during the study. Important changes involving inclusion/exclusion criteria are summarized as follows:

Table 1: Summary of Protocol Amendments

Amendment #/ Date	Original text	Revised text
Amendment #1/Dec-19-2011	Inclusion criteria # 2: Subjects will be healthy males or non-pregnant, non-lactating females at least 18 years of age and older…..etc	Inclusion criteria # 2: Subjects will be healthy males or non-pregnant, non-lactating females at least **12** years of age and older…..etc

Amendment #2/Feb-15-2012	Inclusion criteria # 5: Has sum of the clinical signs and symptoms scores of the target lesion of at least 6, including a minimum score of 2 for erythema and a minimum score of 2 for scaling	Inclusion criteria # 5: Has sum of the clinical signs and symptoms scores of the target lesion of at least **4**, including a minimum score of 2 for erythema and a minimum score of 2 for scaling **or pruritus**
Amendment #2/Feb-15-2012	Subjects will be discontinued from the study and will not be required to return at visit 3 if their baseline cultures are not positive for causative dermatophytes, i.e., *Trichophyton rubrum, trichophyton mentagrophytes, or Epidermophyton floccosum*	Subjects will be discontinued from the study and will not be required to return at visit 3 if their baseline cultures are not positive for causative dermatophytes, i.e., *Trichophyton rubrum, trichophyton mentagrophytes,* ***Trichophyton tonsurans*** *or,* *Epidermophyton floccosum*
Amendment #3 /Apr-10-2012	Inclusion criteria # 2: Subjects will be healthy males or non-pregnant, non-lactating females at least 12 years of age and older…..etc	Inclusion criteria # 2: Subjects will be healthy males or non-pregnant, non-lactating females at least **18** years of age and older…..etc

Note: Amendment #3 reverses the change to inclusion criteria # 2 in Amendment #1

2.2 Data Sources

The data reviewed for this report consisted of data tables in the electronic archives, case report forms, and clinical study report. All tables in this report were independently verified and sources were indicated where applicable. The data reviewed are located under ANDA 205181:

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3 STATISTICAL EVALUATION

Data submitted were adequate and no issue in terms of data quality or analysis was identified by the reviewer.

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study BTNF 1104 was a double-blind, randomized, parallel-group, vehicle-controlled and multicenter study to evaluate the safety and bioequivalence of a generic Butenafine HCI Cream 1% and reference listed Lotrimin Ultra® (Butenafine HCI Cream, 1%), and to determine whether the efficacy of each of the 2 active treatments was superior to that of the vehicle cream in subjects with interdigital tinea pedis. Subjects were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: test, reference or vehicle, respectively. The study enrolled subjects from 20 sites in the US. Subjects applied the study medication 2 times per day for 7 consecutive days. The schedule of study procedures is shown in the following table.

Table 2: Schedule of Study Procedures

Visit Title Visit Number Scheduled Day Scheduling Window	Baseline Visit 1 Day 1 None	End of Treatment Visit 2 Day 8 (+3 days)	Test of Cure/End of Study/Early Discontinuation Visit 3 Day 42 (±4 days)	Unscheduled
Written Informed Consent	X			
Demographic Information	X			
Medical History	X			
Physical Examination (Including Vital Signs)	X			
Urine Pregnancy Test[1]	X		X	X
Prior Medication Review	X			
Diagnosis of Tinea Pedis[2]	X			
Identification of Target lesion	X			
Mycological Evaluations (KOH Wet Mount and Fungal Culture)	X	X	X[3]	X
Investigator Evaluation of Erythema, Scaling, Maceration, and Fissuring/Cracking	X	X	X[3]	X
Subject Evaluation of Pruritus and Burning/Stinging	X	X	X[3]	X
Inclusion/Exclusion Criteria Review	X			
Randomization	X			
Dispense Study Medication and Subject Diary	X			
Subject Instruction/ Compliance Review	X	X	X[4]	X[4]
First Study Medication Application at Study Site	X			
Adverse Events Assessment	X	X	X	X
Concomitant Medication Review		X	X	X
Study Medication and Subject Diary Return, Accountability		X	X[4]	X[4]
Schedule/Confirm Next Visit	X	X		X

[1] For women of childbearing potential (excluding women who were surgically sterilized or postmenopausal for at least 2 years)

[2] Clinical diagnosis and positive potassium hydroxide (KOH) wet mount preparation showing segmented fungal hyphae.

[3] For subjects who had a negative baseline culture and returned for an Early Discontinuation Visit, mycological evaluations and investigator and subject evaluations of signs and symptoms were not applicable.

[4] Collection of previously uncollected subject diary and assessment of compliance and/or study medication and recording of study medication accountability (if applicable).

Source: clinical study report, table 9.3 at page 26

The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved therapeutic cure at Visit3/Day 42 (±4 days). Therapeutic cure was defined as an achievement of both mycological cure (negative KOH wet mount and a negative fungal culture) and clinical cure (total signs and symptoms score no more than 2, with no individual severity score greater than 1 on the 4-point scale). No secondary efficacy endpoint was specified in this study.

Comments: The study design and definition of primary efficacy endpoint follow the recommendation of draft guidance on Butenafine Hydrochloride[1] and, therefore, they are adequate.

3.1.2 Statistical Methodologies

Sponsor's method

Equivalence:
The compound hypothesis to be tested for clinical equivalence between test and reference was:

H_o: P_T-$P_R \leq -0.20$ or P_T-$P_R \geq 0.20$ vs.
H_a: $-0.20 < P_T$-$P_R < 0.20$

where P_T and P_R were the proportions of subjects with therapeutic cure at Visit 3/Day 42 (±4 days) for the test and reference products, respectively.
The test product would be considered bioequivalent to the reference product if the 90% confidence interval on the difference in the proportions of cures , using Wald's method with Yate's continuity correction, was contained within the limits -0.20 to +0.20 for the PP population.

Superiority
The compound hypothesis to be tested for superiority of test and reference over vehicle was

H_o: $P_T \leq P_V$ or $P_R \leq P_V$ vs.
H_a: $P_T > P_V$ and $P_R > P_V$

where P_T, P_R and P_V were the proportions of subjects with therapeutic cure at Visit 3/Day 42 (±4 days) for the test, reference and vehicle products, respectively.
Superiority would be established if the proportion of cures in the active treatment groups was significantly greater than that in the vehicle group in the mITT population, using continuity-corrected Z-tests at 2-sided level of 0.05.

Reviewer's method

Equivalence
Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence. The "cure" at visit 3 in the PP population was the primary outcome for the bioequivalence analysis.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081288.htm

The compound hypothesis to be tested is:

H_o: P_T-P_R < -0.20 or P_T-P_R > 0.20 vs.
H_a: -0.20 ≤ P_T-P_R ≤ 0.20

where P_T and P_R were the cure rate of test and reference products, respectively.
Let n_T = sample size of test treatment group, n_R = sample size of reference treatment group,

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

where $\hat{p}_T$ and $\hat{p}_R$ were the observed cure rates for the test and reference groups, respectively; and *se* was the estimated standard error of $\hat{p}_T$ - $\hat{p}_R$. The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

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

We reject H_0 if L ≥ -0.20 and U ≤0.20. Rejection of H_o supports the conclusion of equivalence of two products.

The applicant's statistical method to establish equivalence and equivalence boundary were adequate. However, the hypothesis was slightly different (≤ vs. < in the H_o) from the one recommended in the draft guidance. The reviewer performed analysis using the same method as the sponsor but drew conclusions based on the hypothesis described in the draft guidance. For superiority testing, Fisher's exact test (at 2-sided level of 0.05) was used for the assessment, in addition to approximate method - continuity-corrected Z-test.

For superiority testing, sensitivity analysis was performed on those subjects with complete data to compare the results from primary mITT population using last observation carried forward (LOCF).

3.1.3 Analysis population

Bioequivalence testing between the test and reference products was conducted in the per-protocol (PP) population, which consists of all subjects randomized, who met all inclusion/exclusion criteria, who had a positive baseline skin fungal culture for *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, or Epidermophyton floccosum,* who were compliant with the assigned study treatment (compliance rate between 75 and 125%) and completed the evaluation at Visit 3/Day 42 (±4 days), who did not take any concomitant medications prohibited by protocol, or who had any other significant protocol violations.

Superiority testing between the test/reference products and control vehicle was conducted in the modified intent-to-treat (mITT) population, which consists of all subjects randomized, who met all inclusion/exclusion criteria, who had a positive baseline skin fungal culture, who applied at least one dose of assigned study medication, and who returned for at least one visit after Visit 1/Day 1.

Safety analyses were conducted in the ITT population, which includes all subjects randomized and given at least one dose of assigned study medication.

Subjects who were discontinued early from the study due to lack of treatment effect after completing 7 days of treatment were analyzed in the mITT and PP populations as treatment failures. Subjects who discontinued early for other reasons were excluded from the PP population, but included in the mITT population, using LOCF.

3.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 3 shows the enrollment and final disposition of subjects, and also reflects the discrepancy between sponsor's and FDA's analysis populations. Seven hundred seven patients were enrolled into the study and randomized to 3 different treatment groups (Test (n=283), Reference (n=283), or Vehicle (n=141)). Most sites enrolled at least 10 patients, except for study centers 11 and 19 that enrolled 7 patients each. 515 patients were eligible for the sponsor's modified Intent-to-Treat (mITT) population; with 201, 211 and 103 patients in the test, reference and vehicle groups, respectively. 469 patients were eligible for the sponsor's Per Protocol (PP) population. Of the 469 patients, 183 were in the test group, 194 were in the reference group, and 92 were in the vehicle group.

The following patients should be removed from the mITT and PP populations based on the recommendations from the clinical reviewer, following the draft guidance:

- (b) (6)

FDA's Per-Protocol (FPP) population consists of 456 patients, with 177, 191 and 88 patients in the test, reference and vehicle groups, respectively. FDA modified ITT (FITT) population consists of 502 patients, with 195, 208 and 99 patients in the test, reference and vehicle groups, respectively. The percentages of patients who completed the study were slightly lower in the vehicle group (95%) compared to the test (97%) and reference (96.15%) groups.

Table 3: Subject Enrollment and Final Study Disposition

	Test	Reference	Vehicle	Total
Enrollment	**283**	**283**	**141**	**707**
Total exclusion from Sponsor's ITT population	0	0	0	0
Total Sponsor's ITT population (ITT)	**283**	**283**	**141**	**707**
Total exclusion from Sponsor's PP population	100	89	49	238
Total Sponsor's PP population (PP)	**183**	**194**	**92**	**469**
Additional exclusion for FDA's PP population				
Prohibited Medication	5	1	0	6

Inclusion criteria violation (<18 years old)	1	1	3	5
Inclusion criteria violation (clinical diagnosis)	0	1	1	2
Exclusion criteria violation (past medical history)	0	0	1	1
Total FDA's PP Population (FPP)	**177**	**191**	**88**	**456**
Total exclusion from sponsor's mITT population	82	72	38	192
Total Sponsor's mITT population	**201**	**211**	**103**	**515**
Additional exclusions for FDA's mITT population				
Prohibited Medication	5	1	0	6
Inclusion criteria violation (<18 years old)	1	1	3	5
Inclusion criteria violation (clinical diagnosis)	0	1	1	2
Exclusion criteria violation (past medical history)	0	0	1	1
Total FDA's mITT population (FITT)	**195**	**208**	**99**	**502**
Number discontinued study	6	8	5	19
Number completed study	189	200	94	483

Duration of study therapy and compliance rate by treatment group are shown in Table 4. The mean duration and compliance rates were comparable among three groups, even with one subject (b) (6) in the reference group taking 50 doses of study therapy (compliance rate = 357.1). This subject was included in the mITT population but not included in the PP population

Table 4: Exposure to Study Drug and Treatment Compliance in the FDA's ITT Population

	Test (N=282)	Reference (N=280)	Vehicle (N=138)
Duration(days)			
Mean± SD	7.59±0.59	7.66±1.29	7.59±0.77
Median	8	8	8
Min-Max	7-10	6-25	4-11
Missing	2	5	2
Compliance rate			
Mean± SD	99.83±4.41	100.64±15.99	99.91±3.54
Median	100	100	100
Min-Max	71.4-121.4	87.5-357.1	86.7-114.3
missing	2	5	2

Age, gender and race by treatment groups in the FITT and FPP populations are shown in Tables 5 and 6. Treatment groups in the two analysis populations were balanced with respect to age, gender and race. Mean ages in two analysis populations were 46 years old, with a range of 45-47 years old in three treatment groups. Males comprised the majority (FITT: 78.1%, FPP: 76.9%). The test group had more male subjects compared to reference group, and both test and reference groups had more male subjects relative to vehicle group. The difference in gender distribution was not statistically significant. The majority of the study population was Caucasians (62-64%) and followed by Blacks (≈33%).

Table 5: Baseline Demographic Characteristics in the FDA's mITT (FITT) Population

Demographic characteristics	Test N=195	Reference N=208	Vehicle N=99	Total N=502	p-value
Age					
Mean ±SD	47.5±15.39	45.9±15.40	44.8±16.20	46.4±15.56	0.1417
Range	19-90	18-92	18-89	18-92	
Gender					
Female (%)	36(18.46)	47(22.60)	27(27.27)	110(21.91)	0.2014
Male(%)	159(81.54)	161(77.40)	72(72.73)	392(78.09)	
Race					
Caucasian (%)	118(60.51)	137(65.87)	60(60.61)	315(62.75)	0.7015
Black (%)	69(35.38)	67(32.21)	38(38.38)	174(34.66)	
Asian (%)	2(1.03)	0(0.00)	1(1.01)	3(0.60)	
American Indian (%)	2(1.03)	3(1.44)	0(0.00)	5(1.00)	
Mixed (%)	3(1.54)	0(0.00)	0(0.00)	3(0.60)	
Other (%)	1(0.51)	1(0.48)	0(0.00)	2(0.39)	

Table 6: Baseline Demographic Characteristics in the FDA's PP (FPP) Population

Demographic characteristics	Test N=177	Reference N=191	Vehicle N=88	Total N=456	p-value
Age					
Mean ±SD	47.7±15.74	46.2±15.55	45.4±16.11	46.6±15.72	0.2503
Range	19-90	18-92	19-89	18-92	
Gender					
Female (%)	34(19.21)	46(24.08)	25(28.41)	105(23.03)	0.1727
Male(%)	143(80.79)	145(75.92)	63(71.59)	351(76.97)	
Race					
Caucasian (%)	113(63.84)	126(65.97)	55(62.50)	294(64.47)	0.8957
Black (%)	57(32.20)	62(32.46)	32(36.36)	151(33.11)	
Asian (%)	2(1.13)	0(0.00)	1(1.14)	3(0.66)	
American Indian (%)	2(1.13)	2(1.05)	0(0.00)	4(0.88)	
Mixed (%)	2(1.13)	0(0.00)	0(0.00)	2(0.44)	
Other (%)	1(0.57)	1(0.52)	0(0.00)	2(0.44)	

Tables 7 and 8 display the baseline study characteristics (KOH, mycological evaluation and clinical assessment of the target site) by treatment groups in the FITT and FPP populations. For all factors examined, we can see that the two analysis populations were comparable. All patients were KOH positive, as required by the inclusion criteria. The majority of the study populations had a positive culture for *T. rubrum* (88.8%), and only one subject had a positive culture for *T. tonsurans* in the FITT population. The severity most frequently reported on clinical assessment was mild fissuring/cracking, moderate erythema, no maceration, moderate scaling, moderate pruritus and no burning/stinging. The mean total signs and symptoms score for the entire combined study population was 8.9. The mycological and clinical assessment results were similar among three treatment groups.

Table 7: Baseline Study Characteristic in FITT Population

Study characteristics N(%)	Test N=195	Reference N=208	Vehicle N=99	Total N=502
KOH				
Positive	195(100)	208(100)	99(100)	502(100)
Negative	0(0)	0(0)	0(0)	0(0)
Mycological culture				
Trichophyton rubrum	175(89.74)	184(88.46)	87(87.88)	446(88.84)
Trichophyton mentagrophytes	13(6.67)	13(6.25)	7(7.07)	33(6.57)
Trichophyton tonsurans, or	0	1(0.48)	0	1(0.20)
Epidermophyton floccosum	7(3.59)	10(4.81)	5(5.05)	22(4.38)
Clinical assessment				
Fissure/cracking				
None (0)	72(36.92)	73(35.10)	37(37.37)	182(36.25)
Mild (1)	81(41.54)	97(46.63)	34(34.34)	212(42.23)
Moderate (2)	39(20.00)	33(15.87)	25(25.25)	97(19.32)
Severe (3)	3(1.54)	5(2.40)	3(3.03)	11(2.19)
Erythema				
None (0)	0	0	0	0
Mild (1)	0	0	0	0
Moderate (2)	172(88.21)	184(88.46)	91(91.92)	447(89.04)
Severe (3)	23(11.79)	24(11.54)	8(8.08)	55(10.96)
Maceration				
None (0)	77(39.49)	91(43.75)	38(38.38)	206(41.04)
Mild (1)	66(33.85)	62(29.81)	28(28.28)	156(31.08)
Moderate (2)	39(20.00)	43(20.67)	26(26.26)	108(21.51)
Severe (3)	13(6.67)	12(5.77)	7(7.07)	32(6.37)
Scaling				
None (0)	0	0	0	0
Mild (1)	1(0.51)	5(2.40)	2(2.02)	8(1.59)
Moderate (2)	134(68.72)	143(68.75)	63(63.64)	340(67.73)
Severe (3)	60(30.77)	60(28.85)	34(34.34)	154(30.68)
Pruritus				
None (0)	22(11.28)	21(10.10)	9(9.09)	52(10.36)
Mild (1)	53(27.18)	45(21.63)	23(23.23)	121(24.10)
Moderate (2)	73(37.44)	100(48.08)	44(44.44)	217(43.23)
Severe (3)	47(24.10)	42(20.19)	23(23.23)	112(22.31)
Burning/stinging				
None (0)	92(47.18)	90(43.27)	45(45.45)	227(45.22)
Mild (1)	57(29.23)	52(25.00)	23(23.23)	132(26.29)
Moderate (2)	35(17.95)	43(20.67)	22(22.22)	100(19.92)
Severe (3)	11(5.64)	23(11.06)	9(9.09)	43(8.57)

Table 7: Baseline Study Characteristic in FITT Population (Continued)

Study characteristics	Test N=195	Reference N=208	Vehicle N=99	Total N=502	p-value
Total signs & symptoms score					
Mean ±SD	8.8±2.44	8.9±2.37	9.1±2.48	8.9±2.42	0.6503
Range	4-16	4-15	5-15	4-16	

Table 8: Baseline Study Characteristic in FPP Population

Study characteristics N(%)	Test N=177	Reference N=191	Vehicle N=88	Total N=456
KOH				
Positive	177(100)	191(100)	88(100)	456(100)
Negative	0(0)	0(0)	0(0)	0(0)
Mycological culture				
Trichophyton rubrum	158(89.27)	169(88.48)	77(87.50)	404(88.59)
Trichophyton mentagrophytes	13(7.34)	13(6.81)	7(7.95)	33(7.24)
Epidermophyton floccosum	6(3.39)	9(4.71)	4(4.55)	19(4.17)
Clinical assessment				
Fissure/cracking				
None (0)	62(35.03)	66(34.55)	29(32.95)	157(34.43)
Mild (1)	77(43.50)	90(47.12)	32(36.36)	199(43.64)
Moderate (2)	35(19.77)	30(15.71)	25(28.41)	90(19.74)
Severe (3)	3(1.69)	5(2.62)	2(2.27)	10(2.19)
Erythema				
None (0)	0	0	0	0
Mild (1)	0	0	0	0
Moderate (2)	158(89.27)	168(87.96)	82(93.18)	408(89.47)
Severe (3)	19(10.73)	23(12.04)	6(6.82)	48(10.53)
Maceration				
None (0)	71(40.11)	81(42.41)	32(36.36)	184(40.35)
Mild (1)	62(35.03)	58(30.37)	27(30.68)	147(32.24)
Moderate (2)	33(18.64)	40(20.94)	24(27.27)	97(21.27)
Severe (3)	11(6.21)	12(6.28)	5(5.68)	28(6.14)
Scaling				
None (0)	0	0	0	0
Mild (1)	1(0.56)	4(2.09)	2(2.27)	7(1.53)
Moderate (2)	124(70.06)	135(70.68)	57(64.77)	316(69.30)
Severe (3)	52(29.38)	52(27.23)	29(32.95)	133(29.17)
Pruritus				
None (0)	18(10.17)	20(10.47)	7(7.95)	45(9.87)
Mild (1)	50(28.25)	42(21.99)	22(25.00)	114(25.00)
Moderate (2)	70(39.55)	90(47.12)	39(44.32)	199(43.64)
Severe (3)	39(22.03)	39(20.42)	20(22.73)	98(21.49)
Burning/stinging				
None (0)	83(46.89)	81(42.41)	40(45.45)	204(44.73)
Mild (1)	52(29.38)	48(25.13)	21(23.86)	121(26.54)
Moderate (2)	32(18.08)	39(20.42)	19(21.59)	90(19.74)
Severe (3)	10(5.65)	23(12.04)	8(9.09)	41(8.99)

Table 8: Baseline Study Characteristic in FPP Population (Continued)

Study characteristics	Test N=177	Reference N=191	Vehicle N=88	Total N=456	p-value
Total signs & symptoms score					
Mean ±SD	8.7±2.43	8.9±2.42	9.2±2.48	8.9±2.43	0.5413
Range	5-16	4-15	5-15	4-16	

3.1.5 Results and Conclusions

3.1.5.1 Sponsor's Results

As shown in Table 9, the test and reference products were bioequivalent with regard to therapeutic cure rate at Visit 3/Day 42 in the PP population (57.9% and 49.5%, respectively; 90% CI of difference in rates: (-0.51%, 17.39%)). The test (55.7%) and reference (48.3%) products were both superior over vehicle (14.6%) for therapeutic cure rate at Visit 3/Day 42 in the mITT population with p<0.0001.

Table 9: Summary of Sponsor's Primary Efficacy Results

Butenafine HCl Cream, 1% Therapeutic Cure[1] Rates at Visit 3/Day 42 Clinical Bioequivalence Study (Study BTNF 1104)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.[2]**
Therapeutic cure, per-protocol population	106/183 (57.9%)	96/194 (49.5%)	N/A	(-0.51%, 17.39%)
	Test	**Reference**	**Vehicle**	**P-value[3]**
Therapeutic cure, modified intent-to-treat population	112/201 (55.7%)	102/211 (48.3%)	15/103 (14.6%)	Test vs Vehicle: $p < 0.0001$ Reference vs Vehicle: $p < 0.001$

1 Therapeutic cure is defined as an achievement of both mycological cure (i.e., negative KOH wet mount and a negative fungal culture) AND clinical cure (i.e., a total severity score of no more than 2 with no individual severity score greater than 1) on a 4-point scale from 0 = none to 3 = severe. Symptoms were erythema, scaling, maceration, fissuring/cracking, pruritus, and burning/stinging.

2 Confidence interval from Wald's method with Yates' continuity correction.

3 P-values for treatment comparisons from two-sided Z-tests with continuity correction.

Source: BioSummary Table for Study BTNF 1104, page 3

3.1.5.2 Reviewer's Results

The findings from the reviewer's analyses were consistent with those from the sponsor's analyses. The discrepancies in numbers reflect the difference between sponsor's and FDA's analysis populations.

Equivalence testing

The test product (58.2%) was bioequivalent to the reference product (49.7%) for therapeutic cure rate at Visit 3/Day42 in the FDA's PP population with the 90% CI on the difference between two rates being (-0.61%, 17.52%). This is within the range of -20% to +20%, demonstrating equivalence.

Table 10: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the FDA's PP Population

	Treatment Group			90% CI for Bioequivalence
	Test	Reference	Vehicle	
FPP Population				
N	177	191	88	
Cure	103 (58.19%)	95 (49.74%)	13 (14.77%)	(-0.61,17.52)
No cure	74 (41.81%)	96 (50.26%)	75 (85.23%)	

Superiority testing

The test (55.9%) and reference (48.56%) products were both superior to vehicle (14.14%) for the therapeutic cure rate at Visit 3/Day 42 in the FDA's mITT population, with $p<0.0001$.

Table 11: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the FDA's mITT Population

	Treatment Group			P-value for Superiority	
	Test	Reference	Vehicle	Test vs Vehicle	Reference vs. Vehicle
FITT Population					
N	195	208	99		
Cure	109(55.90%)	101(48.56%)	14(14.14%)	<.0001*	
No cure	86(44.10%)	107(51.44%)	85(85.86%)		<.0001*

*results from both Fisher's exact and approximate Z tests

17 subjects had missing data at Visit 3 (test: 5, reference: 7, vehicle: 5). Sensitivity analysis was performed on those subjects with complete data, i.e., no LOCF, to compare the results from primary mITT population using LOCF. The results of sensitivity analysis (Table 12) were consistent with those using LOCF. The test (57.4%) and reference (50.25%) products were both superior to vehicle (14.89%) for therapeutic cure rate at Visit 3/Day 42, with $p<0.0001$.

Table 12: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in Subjects with Complete Data, i.e., no LOCF

	Treatment Group			P-value for Superiority	
	Test	Reference	Vehicle	Test vs Vehicle	Reference vs. Vehicle
FITT Population					
N	190	201	94		
Cure	109(57.37%)	101(50.25%)	14(14.89%)	<.0001*	
No cure	81(42.63%)	100(49.75%)	80(85.11%)		<.0001*

*results from both Fisher's exact and approximate Z tests

3.2 Evaluation of Safety

Adverse events (AE) were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. 36 subjects reported treatment-emergent AEs in the study. The event rates were not significantly different among three treatment groups (test: 4.26%, reference: 5.71%, vehicle: 5.80%), and also were not significantly different between test and reference groups, with p-value > 0.05.

Table 13: Number and Percent of Treatment-Emergent AE by Treatment Group

	Test (N=282)	Reference (N=280)	Vehicle (N=138)
TEAE			
Yes	12 (4.26%)	16 (5.71%)	8 (5.80%)
No	270 (95.74%)	264 (94.29%)	130 (94.20%)

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

There was no major statistical issue in this application.

4.2 Conclusions and Recommendations

The findings from reviewer's analyses were consistent with those from sponsor's analyses. For the primary efficacy endpoint – therapeutic cure rate at Visit 3/Day 42 (±4 days), the test product (58.2%) was bioequivalent to the reference product (49.7%) in the FDA's PP population with the 90% CI on the difference between two rates being (-0.61%, 17.52%). This is within the range of -20% to +20%, demonstrating equivalence. The test (55.9%) and reference (48.56%) products were both superior over vehicle (14.14%) in the FDA's mITT population with $p<0.0001$.

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/s/

YU-TE WU
06/11/2014

STELLA C GROSSER
06/12/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM TO REVIEW COMPLETED IN JUNE 2014

ANDA #:	205181
Drug Name:	Generic version of Butenafine Hydrochloride Cream, 1%
Indication(s):	Athlete's foot
Reference Listed Drug:	Lotrimin Ultra® Cream 1% (MSD Consumer Care Inc.)
Applicant:	Taro Pharmaceuticals USA Inc.,
Date(s):	Submitted February 4, 2013
Biometrics Division:	Division of Biometric VI
Statistical Reviewer:	Yu-te Wu, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D., Team Leader
Medical Division:	Division of Clinical Review
Clinical Team:	Sunny Tse, Ph.D., Sarah Seung, Pharm D.
Keywords:	Bioequivalence, superiority, athlete's foot

This memo is an addendum to the original statistical review completed on 6/12/2014 by the statistical reviewer, Yu-te Wu. Based on the findings from FDA OSI's (Office of Scientific Investigation) inspection report, subject (b) (6) (test group) should be removed from both PP and mITT populations for the reason of missing case report form. Tables were updated to reflect this change.

Table 1: Subject Enrollment and Final Study Disposition

	Test		Reference		Vehicle		Total	
	Sponsor	Agency	Sponsor	Agency	Sponsor	Agency	Sponsor	Agency
Patients Enrolled	283	283	283	283	141	141	707	707
Patients Randomized	283	283	283	283	141	141	707	707
Patients Included in mITT Analysis	201	194	211	208	103	99	515	501
Patients Excluded from the mITT	82	89	72	75	38	42	192	206
Patients Included in PP Analysis	183	176	194	191	92	88	469	455
Patients Excluded from PP analysis	100	107	89	92	49	53	238	252

Equivalence testing

The test product (57.95%) was bioequivalent to the reference product (49.74%) for therapeutic cure rate at Visit 3/Day42 in the FDA's PP population with the 90% CI on the difference between two rates being (-0.87%, 17.30%). This is within the range of -20% to +20%, demonstrating equivalence.

Table 2: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the FDA's PP Population

	Treatment Group			90% CI for Bioequivalence
	Test	Reference	Vehicle	
FPP Population				
N	176	191	88	
Cure	102 (57.95%)	95 (49.74%)	13 (14.77%)	(-0.87,17.30)
No cure	74 (42.05%)	96 (50.26%)	75 (85.23%)	

Superiority testing

The test (55.67%) and reference (48.56%) products were both superior to vehicle (14.14%) for the therapeutic cure rate at Visit 3/Day 42 in the FDA's mITT population, with $p<0.0001$.

Table 3: Proportion of Subjects with Therapeutic Cure at Visit3/Day 42 (±4 days) in the FDA's mITT Population

	Treatment Group			P-value for Superiority	
	Test	Reference	Vehicle	Test vs Vehicle	Reference vs. Vehicle
FITT Population					
N	194	208	99		
Cure	108(55.67%)	101(48.56%)	14(14.14%)	<.0001*	
No cure	86(44.33%)	107(51.44%)	85(85.86%)		<.0001*

*results from both Fisher's exact and approximate Z tests

Conclusion

This re-analysis was performed using updated FDA's mITT and PP populations, and the results show slight numerical differences from the original FDA's analyses. The overall conclusions remain the same as those of the original review completed in June 2014.

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/s/

YU-TE WU
09/23/2014
Conclusions remain the same from original review

STELLA C GROSSER
09/23/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

OTHER REVIEW(s)

M E M O R A N D U M

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

DATE: September 8, 2014

TO: Lesley-Anne Furlong, MD
Director (Acting)
Division of Clinical Review
Office of Generic Drugs

FROM: Gajendiran Mahadevan, Ph.D.
GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering ANDA 205-181, Butenafine HCl Cream 1%

At the request of the Division of Clinical Review (DCR), the Division of Bioequivalence and GLP Compliance (DBGLPC) arranged inspections of the clinical portion of the following bioequivalence study:

Study Number: BTNF 1104
Study Title: "A double-blind, randomized, parallel-group vehicle-controlled, multicenter study to evaluate the safety and bioequivalence of a generic Butenafine HCl cream, 1% and reference listed Lotrimin Ultra® (Butenafine HCL cream, 1%) and compare both active treatments to a vehicle control in the treatment of interdigital Tinea Pedis"

Clinical Inspections:

Clinical site inspections for study BTNF 1104 were performed at the following sites:

1. Radiant Research, Pinellas Park, FL

2. Endeavor Clinical Trials, PA, San Antonio, TX

3. Lower Extremity Research, LLC, Melbourne, FL

The inspection at each clinical site included a thorough examination of the protocol, protocol amendments, protocol deviations, study records, informed consent forms, SOPs, IRB approvals, case report forms, and interviews/discussions with the firm's management and staff.

Radiant Research, Pinellas Park, FL

The clinical site inspection at Radiant Research, Pinellas Park, FL was conducted by Gene Gunn (ORA) and Mizanne Lewis (ORA) during February 3-5, 2014. Following the inspection of Radiant Research, no significant issues were observed and no Form FDA 483 was issued.

Endeavor Clinical Trials, PA, San Antonio, TX

The clinical site inspection at Endeavor Clinical Trials, PA, San Antonio, TX was conducted by Joel Martinez (ORA) during March 26-28, 2014. Following the inspection of Endeavor Clinical Trials, no significant issues were observed and no Form FDA 483 was issued.

Lower Extremity Research, LLC, Melbourne, FL

The clinical site inspection at Lower Extremity Research, LLC, Melbourne, FL was conducted by the ORA investigator, Brunilda Torres during March 24-27, 2014. At the conclusion of the inspection at Lower Extremity Research, Form FDA 483 was issued to the clinical investigator, Dr. Robert Dunne (**Attachment-1**). The firm responded to Form FDA 483 by letters dated April 4, 2014 and May 8, 2014 (**Attachment-2**). The Form FDA 483 observations, the firm's responses to Form FDA 483, and our evaluation follow:

1) **An investigation was not conducted in accordance with the investigational plan. Specifically, per protocol inclusion criteria # 5, clinical assessment scores at the**

target site must include 2 for erythema and at least 2 for scaling or pruritus. Clinical assessment completed for Subject # (b) (6) and documented on source document form at study baseline visit dated 6/19/2012, shows a score of 1 for both pruritus and scaling. This subject was initially reported and subsequently confirmed on a data correction form dates 10/11/2012 as meeting inclusion criterion # 5.

The investigator acknowledged the observation and stated that he has been treating subject (b) (6) for well over 10 years. He claims that he scored the subject with "2" for erythema and "2" for scaling and pruritus and incorrectly documented the assessment for scaling as "1" in the source data. The investigator changed the "scaling" score of subject (b) (6) from "1" to "2" on the clinical assessment source document form on October 11, 2012 (112 days after the initial clinical assessment), even though the monitor advised him not to change the information in the source document.

DBGLPC Assessment:

During the inspection, the ORA investigator collected copies of source documents for clinical assessment(**Attachment 3**) that indicated that subject (b) (6) had a score of "2" for erythema and "1" for both scaling & pruritus. Based on these recorded scores in the source documents, subject (b) (6) would not have met the inclusion criteria #5 (at least a score of 2 for scaling or pruritus)for the study. In this reviewer's opinion, the "scaling" score was changed from "1" to "2" to meet the inclusion criteria for subject (b) (6).

Recording of source data should be contemporaneous and altering source records without supporting documentation is not an acceptable practice. Because this was the only known instance where source data were changed, it is unlikely to impact the data obtained from other subjects at the site.

In the opinion of this reviewer, the data generated from subject (b) (6) are unreliable and should be excluded from the bioequivalence assessment.

Recommendations:

Following the evaluation of the inspectional findings, this DBGLPC reviewer recommends excluding the data from subject (b) (6) at Lower Extremity Research, LLC, Melbourne, FL. The remaining subjects from Lower Extremity Research, LLC, Melbourne, FL and all subjects from Radiant Research, Pinellas Park, FL and Endeavor Clinical Trials, PA, San Antonio, TX are acceptable for Agency review.

Gajendiran Mahadevan, Ph.D.
GLP Branch, DBGLPC, OSI

Final Classification:

VAI: Lower Extremity Research, LLC, Melbourne, FL
FEI: 3010453000

NAI: Radiant Research, Inc., Pinellas Park, FL
FEI: 3006424172

NAI: Endeavor Clinical Trials, PA, San Antonio, TX
FEI: 3006115807

CC:
OSI/DBGLPC/Taylor/Bonapace/Dasgupta/Mahadevan/Dejernett/Fenty-Stewart/Nkha/Johnson
OSI/DBGLPC/Haidar/Skelly/Choi
CDER/OGD/DCR/Furlong/Patel

ORA/FLA-DO/Sinninger/Torres/Gunn/Lewis
ORA/DAL-DO/Turcovski/Martinez

Draft: GM 07/23/2014; 09/04/2014
Edit: AD 08/15/2014; 09/05/2014; CB 08/19/2014; 09/05/2014

OSI File: BE6513; O:\BE\EIRCOVER\205181.bio.bu

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Lower Extremity Research, LLC, Melbourne, FL/ANDA 205-181_Butenafine

FACTS: 8710678

ATTACHMENT 1

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/s/

GAJENDIRAN MAHADEVAN
09/08/2014

ARINDAM DASGUPTA
09/08/2014

CHARLES R BONAPACE
09/08/2014

WILLIAM H TAYLOR
09/09/2014

M E M O R A N D U M

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

DATE: October 8, 2013

TO: Director, Investigations Branch
Florida District Office
555 Winderley Place, Suite 200
Maitland, FL 32751

Director, Investigations Branch
Dallas District Office
4040 N. Central Expressway
Dallas, TX 75204

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: FY 2014, **CDER High Priority Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 205-181
DRUG: Butenafine Hydrochloride Cream, 1%
SPONSOR: Taro Pharmaceuticals, Inc., USA

This memo requests that you arrange for inspections of the clinical portions of the following bioequivalence study. Please provide the name of the ORA investigator, once identified, to the DBGLPC point of contact (POC) listed at the end of the assignment. The background material for the assignment will be available in ECMS under the ORA folder. Please complete the inspections prior to March 01, 2014.

<u>Do not</u> reveal the applicant, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections. The sites will receive this information during the inspection opening meetings. Please note that these inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, and not under CP 7348.811 (Clinical Investigators).

At the completion of the inspections, please send a scanned copy of the completed sections A, B & C of this memo to the DBGLPC POC listed at the end of this memo.

Study Number: **BTNF 1104**
Study Title: "A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of a Generic Butenafine HCl Cream, 1% and Reference Listed Lotrimin Ultra® (Butenafine HCl Cream, 1%) and Compare Both Active Treatments to a Vehicle Control in the Treatment of Interdigital Tinea Pedis"

Clinical Site-1: Lower Extremity Research, LLC
2717 N. Wickham Road, Suite 4
Melbourne, FL 32935
Tel: 321-253-6191
Investigator: Robert P. Dunne, DPM

Clinical Site-2: Radiant Research, Inc.
6010 Park Boulevard
Pinellas Park, FL 33781
Tel: 727-544-6367
Investigator: Linda Murray, DO

Clinical Site-3: Endeavor Clinical Trials, PA
8042 Wurzbach, Suite 420
San Antonio, TX 78229
Tel: 210-949-0807
Investigator: Richard A. Pollak, DPM, MS

Please confirm documented informed consent for 100% of subjects enrolled at all the sites. Please audit the subject records at each site and compare the records with the results reported in the ANDA submission. Include a description of your findings in the EIR.

SECTION A

RANDOMIZATION OR BLINDING: Because this is a randomized and blinded bioequivalence study, it is necessary to break the blind and use the treatment codes to verify and confirm that the subjects were dosed according to the treatment randomization schedule. Please verify the following during the inspection:

☐ **Collect a complete copy of the study randomization schedule and blinding code for the site and the dosing logs from the firm/clinical investigator. Unseal the blinding code and note the date and your initials on the envelope. Exhibit a photocopy of the complete randomization schedule and blinding code in the EIR, and include a photocopy with the reserve samples sent to DPA. If the blinding code was already unsealed, determine the reasons why. If a sealed blinding code is not available, please notify the POC immediately.**

☐ **Unblind the treatment codes (e.g., test or reference article) on the Case Report Forms, and use the treatment codes to verify that 100% of the subjects were dosed according to the study randomization schedule. Please scratch off the label covers on the CRF, if needed, to reveal the codes. Document the date and time that you unblind the treatment codes, if applicable.**

☐ **Collect a written statement or affidavit to confirm that the blinding code remained in the possession of the clinical site prior to dosing the initial subject until the FDA inspection, and that the blinding code remained blinded throughout the study. In the event the study related documentation is stored at an alternate site, verify by affidavit that the alternate site is independent of the sponsor, packager and manufacturer.**

SECTION B

RESERVE SAMPLES: Because this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm). Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf).

Please follow the instructions below:

- ☐ **Verify if reserve samples were retained according to regulations.**
- ☐ **If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.**
- ☐ **Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.**
- ☐ **Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:**

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: (314) 539-2135

SECTION C

Data Audit Checklist:

- ☐ Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- ☐ Compare the study records in the ANDA submission to the original documents at the site.
- ☐ Check for evidence of under-reporting of adverse events (AEs).

- ☐ Check for evidence of inaccuracy in the electronic data capture system.

- ☐ Check reports for the subjects audited.
  - o Number of subject records reviewed during the inspection:_____

  - o Number of subjects screened at the site:_____

  - o Number of subjects enrolled at the site:_____

  - o Number of subjects completing the study:_____

- ☐ Verify from source documents that evaluations related to the primary endpoint were accurately reported in the study report.

- ☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

- ☐ Confirm that site personnel followed SOPs during study conduct.

- ☐ Examine correspondence files for any applicant- or monitor requested changes to study data or reports.

- ☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

- ☐ Other Comments:

_____

_____

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the DBGLPC POC for inspection-related questions or clarifications.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of the inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC POC: Chase H. Bourke, Ph.D.
chase.bourke@fda.hhs.gov
Tel: (240)-402-4129
FAX: (301)-847-8748

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Bonapace/Mada/Bourke/Dejernett
OGD/DCR/Patel/Peters
HFR-SW150/Turcovski (DIB)
HFR-SW1540/Martinez (BIMO)
HFR-SE250/Sinninger (DIB) / Torres (BIMO)
Draft: CHB 9/30/2013
Edit: SRM 10/3/2013; SHH 10/4/2013
OSI file BE6513
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/
FACTS: 8710678

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

/s/

CHASE H BOURKE
10/09/2013

CHARLES R BONAPACE
10/10/2013

REGULATORY PROJECT MANAGER'S CLINICAL SITE SELECTION REVIEW FOR OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) INSPECTION

ANDA#	205181
Product	Butenafine Hydrochloride Cream, 1%
Sponsor	Taro Pharmaceuticals USA, Inc.
Study Number and Title	BTNF 1104 A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of a Generic Butenafine HCl Cream, 1% and Reference Listed Lotrimin Ultra® (Butenafine HCl Cream, 1%) and Compare Both Active Treatments to a Vehicle Control in the Treatment of Interdigital Tinea Pedis
Study Dates	First Patient Enrolled: January 12, 2012 Last Patient Completed: August 22, 2012
Submission Date	February 4, 2013
DCR ANDA Reviewer	TBD
Inspection Requestor	Nitin K. Patel, Pharm.D. Medical Affairs Coordinator, Division of Clinical Review (DCR) Office of Generic Drugs
Date of Request/Review	September 4, 2013
Approving Official	John R. Peters, M.D. Director, Division of Clinical Review Office of Generic Drugs

See Attachment for List of Investigators and Sites

SITE NUMBER	HIGH ENROLLMENT PER PROTOCOL POPULATION	HIGH DROPOUTS and EXCLUSIONS	NO INSPECTION HISTORY	LAST INSPECTION VAI & > 5YR	HAS PRIOR INSPECTION HISTORY	DATA UNACCEPTABLE IN PRIOR INSPECTION
1	32				12/2009 VAI at different address in Plano, TX 483 issued	
2	19				✓ Pending 9/2012	
3	17	17/44 ✓			3/2011 NAI	
4	19				6/2011 NAI	
5	18				✓ Pending 8/2012	

6	64 ✓		✓			
7	38				6/2011 NAI	
8	42 ✓				4/2011 VAI 483 issued	
9	14	14/26 ✓			4/2011 NAI	
10	10				2/2008 NAI	
11	2	2/7 ✓	✓			
12	41 ✓		✓			
13	4	4/13 ✓			✓ Pending 2/2013	
14	30				✓ Pending 8/2013	
15	48 ✓		✓			
16	8				✓ Pending For-Cause 9/2012 ANDA 203792	Robert T. Matheson, MD. 7/2011: OSI recommended excluding data from BE evaluations. The blinding code was not maintained at the site.
17	15	15/35 ✓			1/2013 VAI for different investigator (Michelle Chambers) at same address 483 issued	
18	34				1/2013 NAI	
19	1	1/7 ✓			2/2010 NAI	
20	15				3/2012 VAI 483 issued	

RECOMMENDATION:

The following clinical investigators have no prior inspectional history and will be included in the Request for Biopharmaceutical Inspections Consult Form to OSI:

SITE NUMBER	**Investigator**	**Per Protocol Population**
6	Robert P. Dunne, DPM Lower Extremity Research, LLC 2717 N. Wickham Road, Suite 4 Melbourne, FL 32935	64
12	Linda Murray, DO Radiant Research, Inc. 6010 Park Boulevard Pinellas Park, FL 33781	41
15	Richard A. Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, TX 78229	48

ATTACHMENT

List of Investigators and Sites

Site No.	Principal Investigator Site Address	Per Protocol Population
01	Jeffrey M. Adelglass, MD Research Across America 9 Medical Parkway Plaza 4, Suite 202 Dallas, TX 75234	32
02	Joe Blumenau, MD Research Across America 9 Medical Parkway Professional Plaza 4, Suite 202 Dallas, TX 75234	19
03	Suzanne Bruce, MD Suzanne Bruce and Associates The Center for Skin Research 1900 St. James Place, Suite 650 Houston, TX 77056	17
04	Eduardo Tschen, MD, MBA Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	19
05	Scott D. Clark, MD Longmont Clinic, PC 1925 W. Mountain View Avenue Longmont, CO 80501	18
06	Robert P. Dunne, DPM Lower Extremity Research, LLC 2717 N. Wickham Road, Suite 4 Melbourne, FL 32935	64
07	Francisco Flores, MD FXM Research Miramar 3000 SW 148th Ave. Suite 216 Miramar, FL 33027	38
08	Michael T. Jarratt, MD DermResearch, Inc. 8140 N. Mopac, Bldg 3, Suite 120 Austin, TX 78759	42
09	Terry M. Jones, MD J&S Studies, Inc. 1710 Crescent Pointe Pkwy College Station, TX 77845	14
10	Steven E. Kempers, MD Minnesota Clinical Study Center 7205 University Avenue NE Fridley, MN 55432	10

Site No.	Principal Investigator Site Address	Per Protocol Population
11	Samuel N. Lederman, MD Altus Research, Inc. 4671 S. Congress Avenue, Suite 100B Lake Worth, FL 33461	2
12	Linda Murray, DO Radiant Research, Inc. 6010 Park Boulevard Pinellas Park, FL 33781	41
13	Adnan Nasir, MD, PhD Wake Research Associates 3100 Duraleigh Road, Suite 304 Raleigh, NC 27612	4
14	Michael J. Noss, MD Radiant Research, Inc. 11500 Northlake Drive, Suite 320 Cincinnati, OH 45249	30
15	Richard A. Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, TX 78229	48
16	Robert T. Matheson, MD Oregon Medical Research Center, PC 9495 SW Locust Street, Suite G Portland, OR 97223	8
17	Douglas R. Schumacher, MD Radiant Research, Inc. 1275 Olentangy River Road, Suite 202 Columbus, OH 43212	15
18	Heather Woolery-Lloyd, MD[1] Tory Sullivan, MD, PA 16100 NE 16th Avenue, Suite A N. Miami Beach, FL 33162	34
19	Zoe Diana Draelos, MD Dermatology Consulting Services 2444 North Main Street High Point, NC 27262	1
20	David C. Wilson, MD The Education and Research Foundation, Inc. 2095 Langhorne Road Lynchburg, VA 24501	15

1 (Site # 18)Tory Sullivan, MD was the principal investigator initially; obligations were transferred to Dr. Woolery-Lloyd when Dr. Sullivan was on a leave of absence.

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

/s/

NITIN K PATEL
09/04/2013

JOHN R PETERS
09/04/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205181

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 205181
APPLICANT: Taro Pharmaceuticals USA, Inc.
RELATED APPLICATION(S):

DRUG NAME: **Butenafine Hydrochloride**
DOSAGE FORM: Cream, 1%

LETTER DATE: 2/4/2013
RECEIVED DATE: 2/4/2013

☐ P-IV
☒ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST: MaPP 5240.1 or MaPP 5240.3 or GDUFA (Approved/Denied)
☐ PEPFAR
☐ PET

Electronic or Paper Submission: Gateway Type II DMF# 019551

BASIS OF SUBMISSION:
NDA: 021307
FIRM: SCHERING PLOUGH HEALTHCARE PRODUCTS INC
RLD: LOTRIMIN ULTRA

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: **DC1 Team 13** ☒ **Activity**	Bio Team: **DBE Team 10, Utpal Munshi** ☒ **Activity**
RPM: **Trang Tran** ☒ **FYI**	Bio PM: Diana Solana-Sodeinde ☒ **FYI**
CHEM PQRPM: **Tania Mazza** ☒ **FYI**	Division of Clinical Review: **DCR** ☒ **Activity**
CHEM Team Leader: James Fan **No Assignment Needed in DARRTS**	DMF Review Team Leader: ☒ **FYI Dave Skanchy**
Labeling Reviewer: **Beverly Weitzman** ☒ **Activity**	Micro Review: ☐ **Activity**
SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):	

Regulatory Reviewer: Shannon Hill Date: **August 22, 2013**	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

Comments: EC-1
Therapeutic Code: 4020120 (Fungicides/Antidermatophyte Agents (Topical))
On Cards: Yes
Archival copy: Gateway
Sections: I

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
- **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**

1. Edit Application Property Type in DARRTS where applicable for

a. First Generic Received
☒ Yes ☐ No
b. Market Availability
☐ Rx ☒ OTC
c. Pepfar
☐ Yes ☒ No
d. Product Type
☐ Small Molecule Drug
e. USP Drug Product (at time of filing review)
☐ Yes ☒ No

2. Edit Submission Patent Records in DAARTS
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. EER (internal notation: RSB to submit at time of filing)
   ☒ Yes
5. GDUFA Obligation Met (Filing Fee, Type II DMF Fee, and Facility Fee)
   ☒ Yes - (internal notation-if not met contact: cder-om-collection@fda hhs.gov)
6. DMF Complete Assessment
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Ask applicant to confirm the selection of option C on FDA form 3674; *received 8/15/2013 (changed to option B)*
2. Ask applicant to resubmit the exclusivity statement to remove qualifier, "in the opinion and to the best of its knowledge"; *received 8/15/2013*
3. Remind applicant to submit the ***annotated*** side by side labeling comparison of container(s) and carton(s) in appropriate section of the checklist (1.14.1.2 versus 1.14.1.3) in future submissions; *acknowledged 8/15/2013*
4. Remind applicant to submit module 2.3 in the specified order outlined on the checklist in future submissions; *acknowledged 8/15/2013*
5. Ask applicant to submit the Validation of Analytical Procedures for the following excipients: polyoxyethylene (23) cetyl ether & propylene glycol dicaprylate; *received 8/15/2013*
6. Ask applicant to resubmit accelerated stability data to include the initiation dates and the pull dates from the stability chamber for each testing time point; *received 8/15/2013*
7. Ask applicant to explain their justification for the level of polyoxyethylene (23) cetyl ether in the proposed composition; the ANDA indicates [redacted] (b) (4) *received 8/15/2013*
8. Spoke with Kavita Srivastava on 8/8/2013

DIVISION OF CLINICAL REVIEW CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA#	205181
DRUG NAME	Butenafine HCl Cream, 1%
DOSAGE FORM	Topical Cream
APPLICANT NAME	Taro Pharmaceuticals USA, Inc.
REFERENCE LISTED DRUG (RLD)	Lotrimin® Ultra (butenafine HCl) Cream 1%
NDA	021307, approved 12/7/01, Schering Plough
PRIMARY REVIEWER	Carol Y. Kim, PharmD. Division of Clinical Review Office of Generic Drugs
SECONDARY REVIEWER	John R. Peters, M.D. Division of Clinical Review Office of Generic Drugs
REQUESTED BY	Edward Washington Regulatory Support Team Office of Generic Drugs
REQUESTED DATE	2/14/13

	Summary of Findings by Division of Clinical Review
X	**Study meets statutory requirements** **Please see comments to be conveyed to the sponsor for details.**
	Study does NOT meet statutory requirements **Reason:**
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: _X__COMPLETE ___INCOMPLETE

Comments to be conveyed to the sponsor:

Your clinical endpoint bioequivalence study is acceptable for receiving your ANDA. The following additional information is requested for the review:

1. **Curriculum Vitae for principal and sub-investigators or equivalent summaries of training and experience relevant to the performance of the clinical study**
2. **Copy of IRB approval letters with dates for protocol, protocol amendments and consent forms**

MODULE 1: ADMINISTRATIVE

		COMMENT (S)
1.1	**1.1.2** **Signed and Completed Application Form (356h)** (Rx/OTC Status) OTC (original signature) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **** PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING****	
1.2	**Cover Letter** Yes	
1.2.1	**Form FDA 3674 (PDF)** B	
*	**Table of Contents** (paper submission only) N/A	
1.3.2	**Field Copy Certification** 21CFR 314.94(d)(5) (original signature) N/A	
1.3.3	**Debarment Certification-GDEA** (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes	
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) N/A	
1.3.5	**Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **Patent Certification [**21 CFR 314.94 (a)(12)/505(j)(2)(A)(vii)] 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ Statement of Notification (21 CFR 314.95/505(j)(B)(i)) ☐ 3. Expiration of Patent(s): a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: State marketing intentions? Yes, no unexpired exclusivities listed **Patent and Exclusivity Search Results from query on Appl No 021307 Product 001 in the OB_OTC list.** **Patent Data** **There are no unexpired patents for this product in the Orange Book Database.** **Exclusivity Data** **There is no unexpired exclusivity for this product.**	
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# 019551 c. Type III DMF authorization letter(s) for container closure Yes; (b) (4) d. Type III or IV DMF authorization letter(s) for sterile product sterilization process N/A 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	

	(b) (4) 	
1.12.4	**Request for Comments and Advice** - Proprietary name requested No If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes N/A 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	**Basis for Submission** NDA#: 021307 Ref Listed Drug: LOTRIMIN ULTRA Firm: SCHERING PLOUGH HEALTHCARE PRODUCTS INC **ANDA suitability petition required?** N/A If Yes, provide petition number and copy of approved petition **ANDA Citizen's Petition Required?** N/A If Yes, provide petition number and copy of petition	
1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Justified 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD	
1.12.14	**Environmental Impact Analysis Statement** **(**cite 21CFR 25.31 and 25.15(d), if applicable) Yes	
1.12.15	**Request for Waiver** (cite 21 CFR 320.22 or 320.24(b)(6)) Request for Waiver of In-Vivo BA/BE Study(ies) N/A	
1.14.1	**Draft Labeling** (Multi Copies N/A for E-Submissions) **1.14.1.1** 4 copies of draft for paper submission only (each strength and container) Yes **1.14.1.2** Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically Yes **1.14.1.4** Labeling Comprehension Studies Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf	
	Listed Drug Labeling **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated N/A **1.14.3.3** RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label Yes	

		COMMENT (S)
2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Yes **Word Processed e.g., MS Word** Yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR)** Yes **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability **2.3.P Drug Product** Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product **Oral Solids**: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft *Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	

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MODULE 2.7: Clinical Summary

		COMMENT (S)
2.7	**Clinical Summary (Bioequivalence)**Model BE Data Summary Tables **http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf** **E-Submission: PDF** Yes **Word Processed: e.g., MS Word** Yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation N/A Table 6. Formulation Data Yes Table 10. Study Information N/A Table 11. Product Information Yes Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products N/A **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution N/A (include complete comparative In Vitro Dissolution Data (individual) with Certificate of Analysis [CoA] for Test and Reference products including: potency, assay, content uniformity, date of manufacture and lot number) Table 9. Reanalysis of Study Samples N/A Table 12. Dropout Information Yes Table 13. Protocol Deviation Yes Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis N/A **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. A - Statistical Summary of the Comparative BA Data For Unscaled Average N/A **- OR -** B - Statistical Summary of the Comparative BA Data For Reference-scaled Average BE Studies N/A Table 16. Composition of Meal Used in Fed Bioequivalence Study N/A **2.7.1.4 Appendix** Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples N/A **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies Yes	

MODULE 3: 3.2.S DRUG SUBSTANCE

		COMMENT (S)
3.2.S.1	**General Information**) Yes (Do not refer to DMF) **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	

3.2.S.2	**Manufacturer** **Drug Substance (Active Pharmaceutical Ingredient)** Must correlate to the establishment information submitted in annex to Form FDA 356h. 1. Name and Full Address(es)of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent's name (if applicable) Yes 4. Specify Function or Responsibility Yes 5. Type II DMF number for API Yes 6. CFN, FEI or DUNS numbers (if available) Yes	
3.2.S.3	**Characterization** Yes Provide the following in tabular format: 1. Name of Impurity(ies) 2. Structure of Impurity(ies) 3. Origin of Impurity(ies)	

Name and Address	Responsibility
(b) (4)	
Taro Pharmaceuticals Inc. 130 East Drive Brampton, Ontario Canada, L6T 1C1 FDA Drug Establishment Registration Number: 3002808318 Contact: Lul Ogba-Ghebriel, Director Regulatory Affairs Tel: (b) (6) Fax: 905-791-0236 E-mail: Lul.Ogba-Ghebriel@taro.ca US Contact Person: Kavita Srivastava, Executive Director, Regulatory Affairs Phone: 914-345 – 9001 ext. (b) (6) Fax: 905-791-0236 E-mail: Kavita.Srivastava@taro.com	(b) (4)

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) Yes **3.2.S.4.2 Analytical Procedures** Yes **3.2.S.4.3 Validation of Analytical Procedures** (API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) Yes 1. Spectra and chromatograms for reference standards and test samples Yes; *refer to 3.2.S.4.4* 2. Samples-Statement of Availability and Identification of: a. Drug Substance Yes b. API lot numbers **Samples Statement** **[21 CFR 314.50(e)(1)]** **Upon request, samples of the following lots of drug substance, Butenafine Hydrochloride and applicable reference standards with appropriate identification, will be made available.** **Butenafine Hydrochloride: Lot # RD-RM11020** (b) (4) **3.2.S.4.4 Batch Analysis** 1. COAs specifications and test results from drug substance mfgr(s) Yes 2. Drug Product manufacturer's Certificates of analysis Yes **3.2.S.4.5 Justification of Specification** Yes	
3.2.S.5	**Reference Standards or Materials** (Do not refer to DMF) Yes	
3.2.S.6	**Container Closure Systems** N/A; refer to DMF# 19551	
3.2.S.7	**Stability** 1. Retest date or expiration date of API N/A; refer to DMF# 19551	

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition with indication of the function of the inactive ingredient(s) Yes 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Yes 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) Yes 4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable) N/A 5. Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration N/A	
3.2.P.2	**Pharmaceutical Development** 1. Pharmaceutical Development Report Yes 2. Microbial Attributes a. Container/Closure Integrity Testing Report for Sterile Products	

b. Antimicrobial Effectiveness Testing for Multi-dose sterile products

3.2.P.3 Manufacture

3.2.P.3.1 Drug Product

Must correlate to the establishment information submitted in annex to From FDA 356h for the finished dosage manufacturer and all outside contract testing laboratories.

1. Name and Full Address(es)of the Facility(ies) Yes
2. Contact name, phone and fax numbers, email address Yes
3. U.S Agent's name (if applicable) N/A; applicant contact is in the U.S.
4. Specify Function or Responsibility Yes
5 CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes
6. CFN, FEI or DUNS numbers (if available) Yes

Name and Address	Responsibility (e.g., fabrication, packaging, labeling, testing, importing, storage and distribution)
Taro Pharmaceuticals Inc. 130 East Drive Brampton, Ontario Canada, L6T 1C1 FDA Drug Establishment Registration Number: 3002808318 Contact: Lul Ogbaghebriel, Director Regulatory Affairs Tel: (b) (6) Fax: 905-791-0236 e-mail: Lul.Ogba-ghebriel@taro.ca	(b) (4)
Taro Pharmaceuticals U.S.A. Inc. Three Skyline Drive Hawthorne, NY 10532	
Taro Pharmaceuticals U.S.A Inc. One Commerce Drive Cranbury, NJ 08152 Contact : Kavita Srivastava, Executive Director, Regulatory Affairs Tel: 914-345-9001, ext. (b) (6) Fax: 914-593-0078 Email: kavita.srivastava@taro.com	Storage and distribution site in U.S.A. of the Drug Product Butenafine Hydrochloride Cream, 1%.

Taro Pharmaceuticals Inc. is identified and known to the FDA as "Site or Firm Establishment Registration No. 3002808318, and has Labeler Code (b) (4) Taro's drug product manufacturing facility at 130 East Drive, Brampton, Ontario, Canada was inspected by the FDA between February 7 - 11, 2011 and the facility was found acceptable.

(b) (4)

[redacted]

3.2.P.3.2 Batch Formula Yes

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process and (for aseptic fill products) Facility Yes

	2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes 3. Master packaging records for intended marketing container(s) Yes 4. If sterile product N/A 5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes **3.2.P.3.4 Controls of Critical Steps and Intermediates** Yes **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A PROPOSED COMMERCIAL BATCH SIZE: B320160B.01X | B321600SY.01X Version 1 June 21, 2011 | Version 1 November 22, 2012 (b) (4) **Quantity per ANDA batch** | **Quantity per Scale-up batch**	
3.2.P.4	**Controls of Excipients** (Inactive Ingredients) Source of inactive ingredients identified Yes **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Yes 2. Suppliers' COA (specifications and test results) Yes **3.2.P.4.2 Analytical Procedures** USP/NF **3.2.P.4.3 Validation of Analytical Procedures** N/A **3.2.P.4.4 Justification of Specifications:** 1. Applicant COA Yes	

MODULE 3: 3.2.P DRUG PRODUCT (Continued)

		COMMENT (S)
3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Yes **3.2.P.5.2 Analytical Procedures** Yes **3.2.P.5.3 Validation of Analytical Procedures** (if using USP procedure, must provide verification of USP procedure) Yes Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Yes 2. Lot numbers and strength of Drug Products **Samples Statement** **[21 CFR 314.50(e)(1)]** Upon request, samples of the following lots of finished drug product, Butenafine Hydrochloride Cream, 1%, and applicable reference standards with appropriate identification will be made available. Butenafine Hydrochloride Cream, 1% Lot: S229-60052 Pack Sizes: 12 g, 15 g, 24 g, and 30 g tubes (b) (4)	

	3.2.P.5.4 Batch Analysis Certificates of Analysis for Finished Dosage Form Yes **3.2.P.5.5 Characterization of Impurities** N/A; *refer to 3.2.S.3.2* **3.2.P.5.6 Justification of Specifications** Yes	
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Yes 2. Components Specification and Test Data Yes 3. Packaging Configuration and Sizes Yes 4. Container/Closure Testing (recommended additional testing for all plastic)N/A a. Solid Orals: water permeation, light transmissionN/A b. Liquids: leachables, extractables, light transmissionN/A 5. Source of supply and suppliers address Yes	
3.2.P.8	**3.2.P.8.1 3.2.P.8.1 Stability and Conclusions (Finished Dosage Form)** 1. Stability Protocol submitted Yes 2. Expiration Dating Period for Marketed Packaging 24 months 3. Expiration Dating Period for Bulk Packaging (if applicable) N/A **3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment** **(From Applicant and Drug Product Manufacturer, if different entities)** Post Approval Stability Protocol and Commitments Yes **3.2.P.8.3 Stability Data** 1. Accelerated stability data a. Four (4) time points 0,1,2,3 Yes **-OR-** b. Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products*, dated June 2013 ****THIS WILL BE REQUIRED AS OF JANUARY 2 2014**** N/A c. For liquid and semi-solid products, upright and inverted/horizontal storage orientation N/A 2. Batch numbers on stability records the same as the test batch Yes 3. Date accelerated stability study initiated Yes 4. Date accelerated stability sample(s) removed from stability chamber for each testing time point Yes	

Table below contains the information on the accelerated stability data (40±2°C, 75±5% RT) for the batch of Butenafine Hydrochloride Cream, 1% Lot # S229-60052, from the original ANDA submission. The information includes the requested initiation dates and the pull dates from the stability chamber for each testing time point.

Testing Point	Batch Manufacturing Date	Packaging Date	Initiation Date	Due Date	Pull Date	Test Date
Initial Analysis	July 4, 2011	July 15, 2011	Jul 18, 2011	Jul 18, 2011	Jul 18, 2011	Jul 23, 2011
1-Month			Jul 18, 2011	Aug 18, 2011	Aug 18, 2011	Aug 22, 2011
2-Month			Jul 18, 2011	Sep 18, 2011	Sep 20, 2011	Sep 28, 2011
3-Month			Jul 18, 2011	Oct 18, 2011	Oct 18, 2011	Oct 26, 2011
6-Month			Jul 18, 2011	Jan 18, 2012	Jan 18, 2012	Jan 26, 2012

Please note that the stability data for accelerated condition is not updated to include the 'Pull date'. This is due to the fact that the Accelerated (40°C) samples are pulled on the 'Due date' or within 3 days after due date, in accordance with SOP.

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	**3.2.R.1.S Executed Batch Records for drug substance (if available)** N/A **3.2.R.2.S Comparability Protocols** N/A **3.2.R.3.S Methods Validation Package** Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Yes  (b) (4) Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) N/A b. Bulk Package Stability (3.2.P.8)	

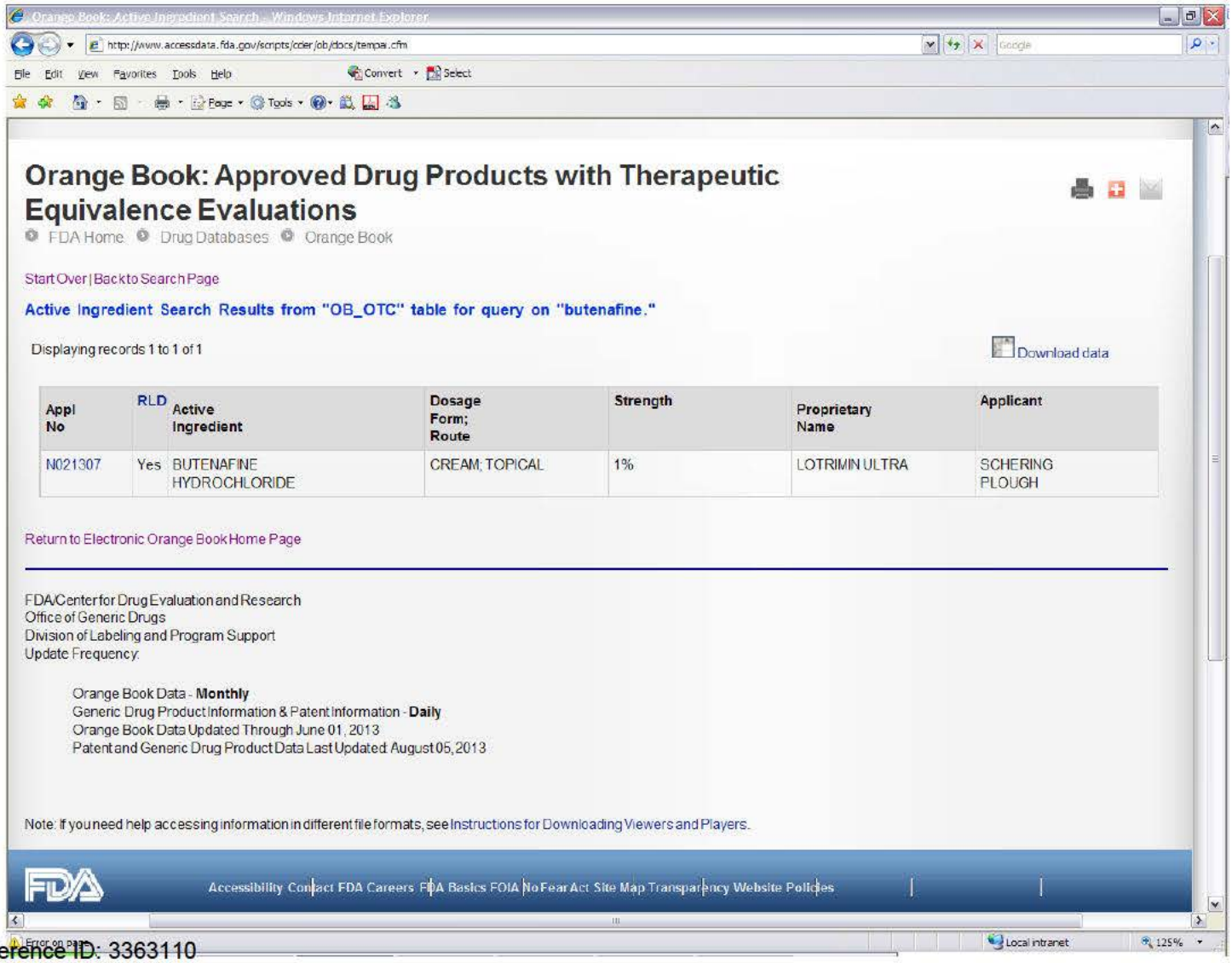
	1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months N/A 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months N/A c. Bulk Package Container and Closure information (3.2.P.7) N/A **3.2.R.1.P.2 Information on Components** Yes **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

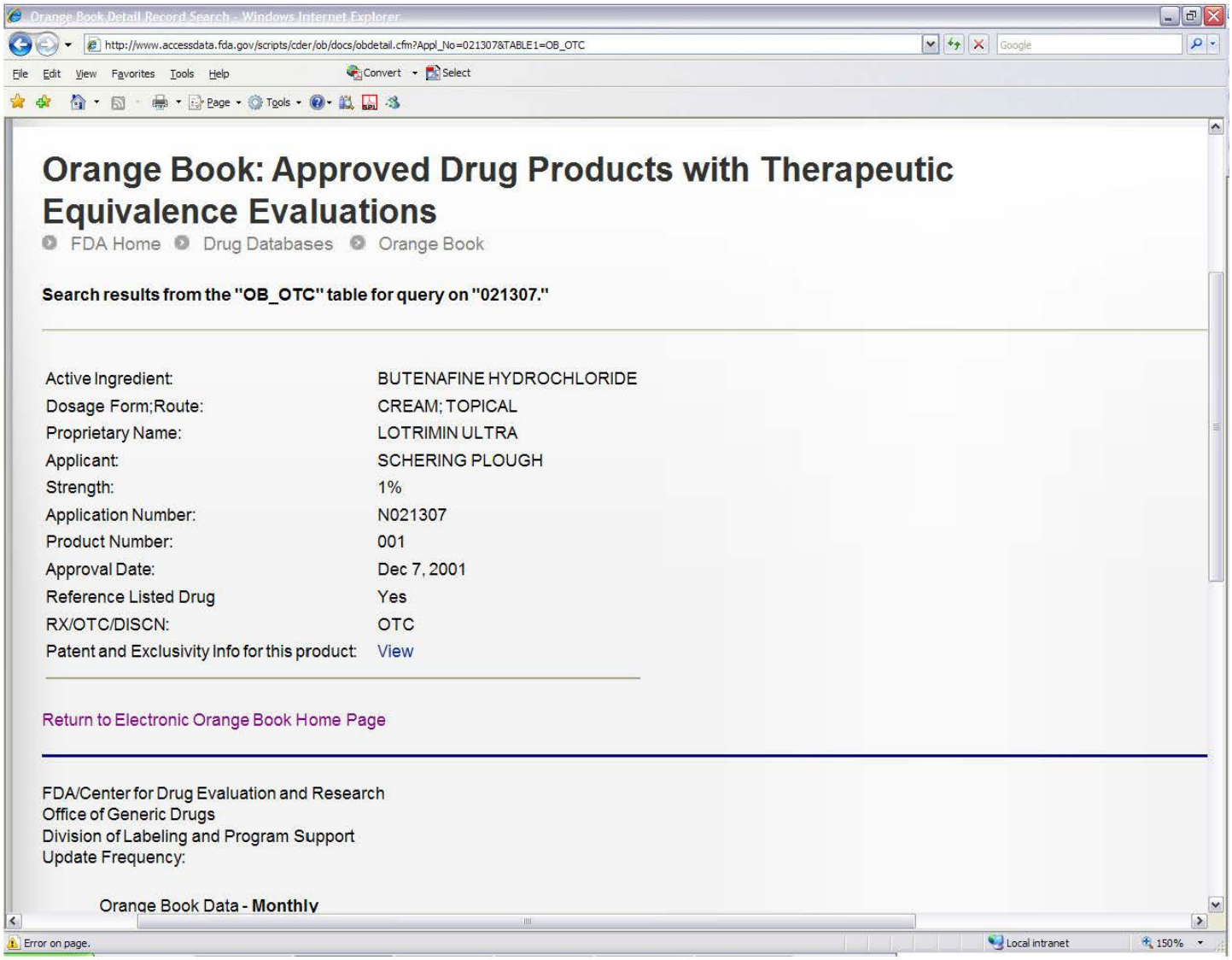
MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	**Tabular Listing of Clinical Studies** Yes	
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) Yes **2. Lot Numbers and strength of Products used in BE Study(ies)** ANDA: S229-60052 RLD: 1H02DA **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	
	See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16. **The study data that support the BA/BE summary tables should be provided in the corresponding sections below:** **5.3.1.2 Comparative BA/BE Study Reports** **5.3.1.3 In Vitro-In-Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7)** **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies** **Case Report Forms** should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** Division of Clinical Review Consult Complete ☐ Yes ☐ No	

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** **Refer to the attached links for Nasal Product BE Tables:** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf **AND** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** Division of Clinical Review Consult Complete ☐ Yes ☐ No	

Updated 7/8/2013

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File Edit View Favorites Tools Help
Convert Select
Page Tools
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
FDA Home Drug Databases Orange Book
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Dosage Form;Route: CREAM; TOPICAL
Proprietary Name: LOTRIMIN ULTRA
Applicant: SCHERING PLOUGH
Strength: 1%
Application Number: N021307
Product Number: 001
Approval Date: Dec 7, 2001
Reference Listed Drug Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: View
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Office of Generic Drugs
Division of Labeling and Program Support
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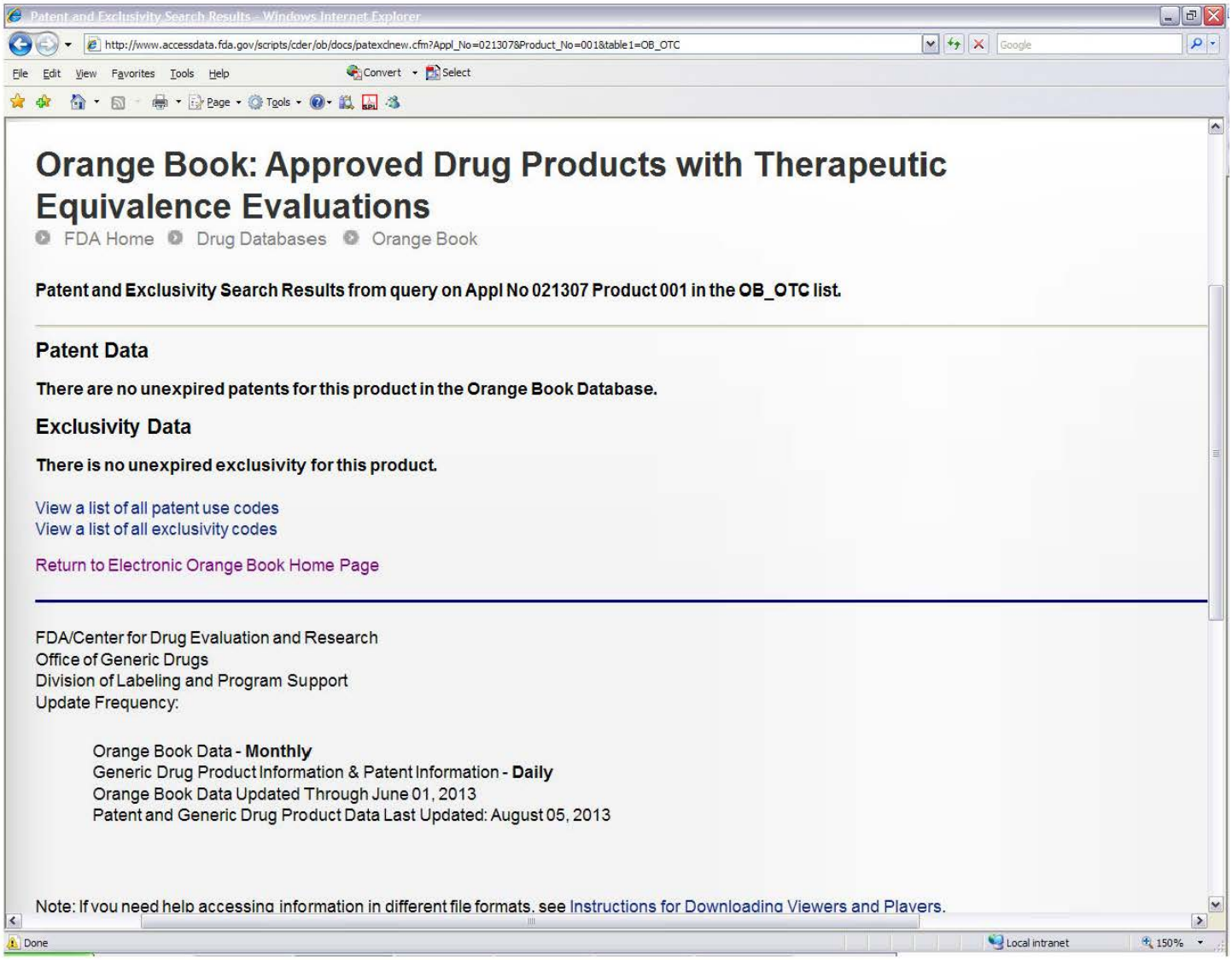
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Convert Select
Page Tools
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
FDA Home Drug Databases Orange Book
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Patent Data
There are no unexpired patents for this product in the Orange Book Database.
Exclusivity Data
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through June 01, 2013
Patent and Generic Drug Product Data Last Updated: August 05, 2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
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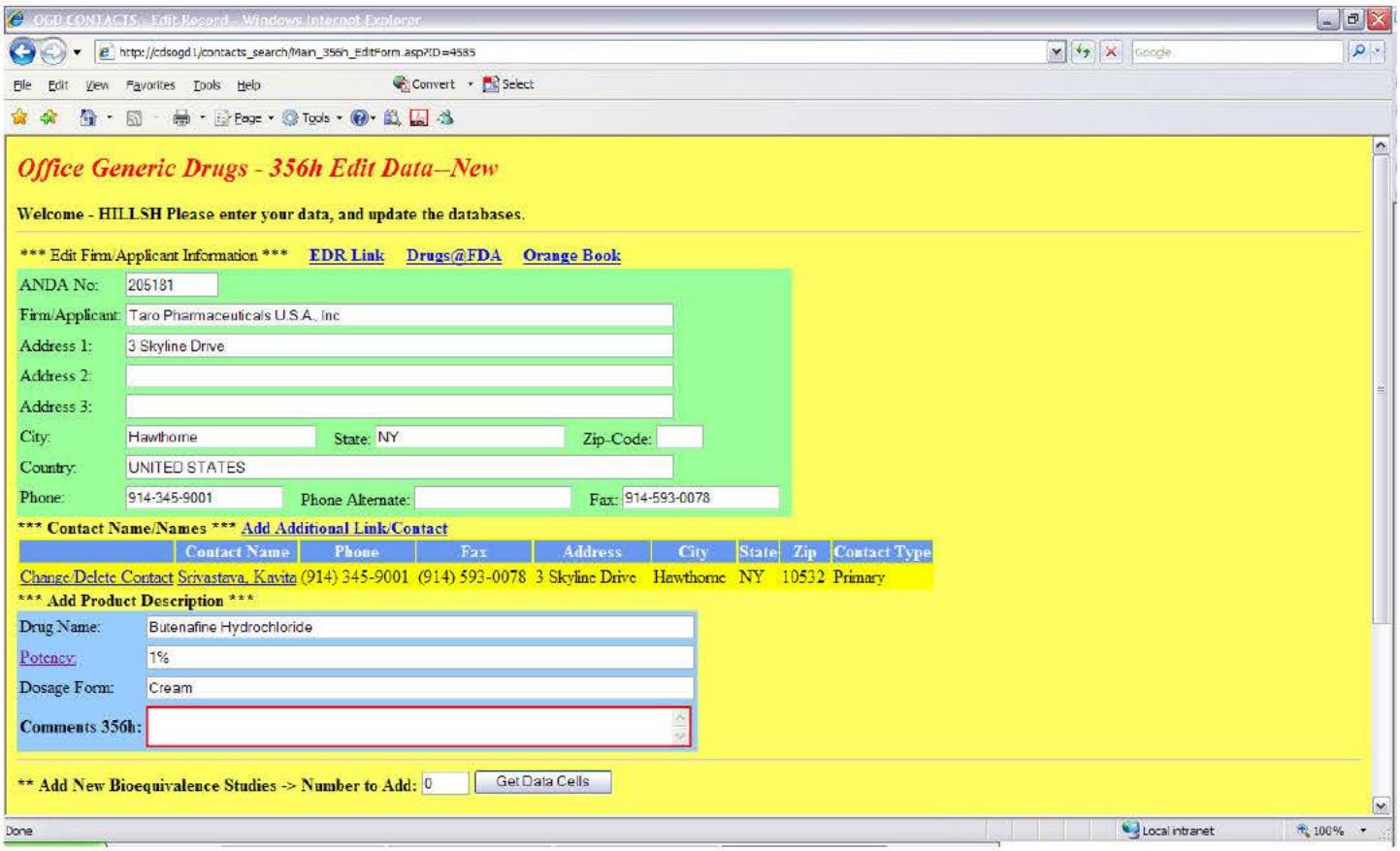
150%

Table 1: Composition of Butenafine Hydrochloride Cream, 1%

Strength (Label claim)	**1%**			
Ingredient	**Quality Standard**	**Quantity (% w/w)**	**mg/g**	**Function**
Butenafine Hydrochloride	Taro	1.000	10.00	Active Pharmaceutical Ingredient
White Petrolatum	USP	[redacted] (b) (4)		
Cetyl Alcohol	NF			
Stearic Acid	NF			
Glyceryl Monostearate SE	Taro			
Propylene Glycol Dicaprylate	Taro			
Purified Water	USP			
Glycerin	USP			
Polyoxyethylene (23) Cetyl Ether	Taro			
Trolamine	NF			
Sodium Benzoate	NF			
Benzyl Alcohol	NF			
Total theoretical weight	--	100.00	1000.0	---

JUSTIFICATION OF INACTIVE INGREDIENTS:

[redacted] (b) (4)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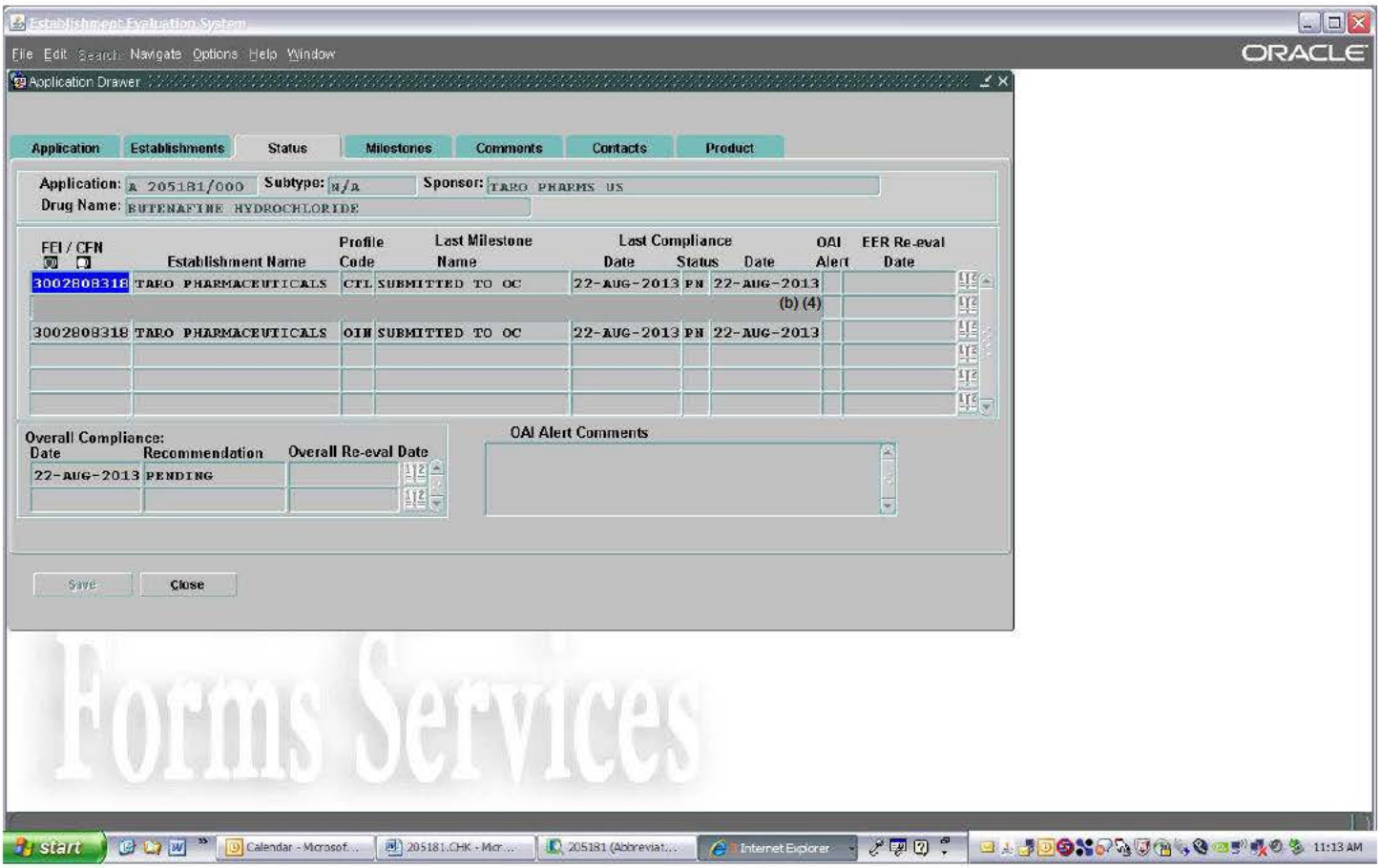
Office Generic Drugs - 356h Edit Data–New
Welcome - HILLSH Please enter your data, and update the databases.
*** Edit Firm/Applicant Information *** EDR Link Drugs@FDA Orange Book
ANDA No: 205181
Firm/Applicant: Taro Pharmaceuticals U.S.A., Inc
Address 1: 3 Skyline Drive
Address 2:
Address 3:
City: Hawthorne State: NY Zip-Code:
Country: UNITED STATES
Phone: 914-345-9001 Phone Alternate: Fax: 914-593-0078
*** Contact Name/Names *** Add Additional Link/Contact
Contact Name | Phone | Fax | Address | City | State | Zip | Contact Type
Change/Delete Contact Srivastava, Kavita (914) 345-9001 (914) 593-0078 3 Skyline Drive Hawthorne NY 10532 Primary
*** Add Product Description ***
Drug Name: Butenafine Hydrochloride
Potency: 1%
Dosage Form: Cream
Comments 356h:
** Add New Bioequivalence Studies -> Number to Add: 0 Get Data Cells
Done
Local intranet
100%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ORACLE
Application Drawer
Application Establishments Status Milestones Comments Contacts Product
Application: A 205181/000 Subtype: N/A Sponsor: TARO PHARMS US
Drug Name: BUTENAFINE HYDROCHLORIDE
FEI / CFN | Establishment Name | Profile Code | Last Milestone Name | Last Compliance Date | Last Compliance Status | Last Compliance Date | OAI Alert | EER Re-eval Date
3002808318 TARO PHARMACEUTICALS CTL SUBMITTED TO OC 22-AUG-2013 PN 22-AUG-2013
(b) (4)
3002808318 TARO PHARMACEUTICALS OIH SUBMITTED TO OC 22-AUG-2013 PN 22-AUG-2013
Overall Compliance: Date | Recommendation | Overall Re-eval Date
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OAI Alert Comments
Save Close
Forms Services
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Internet Explorer
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHANNON L HILL
08/26/2013

MARTIN H Shimer
08/27/2013

CHECKLIST FOR THE CHEMISTRY REVIEW:

ANDA 205181, Butenafine Hydrochloride Cream, 1%

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	RBPM RH 11/1/2017	☐ Yes ☒ No
DMF adequate? 019551, Butenafine Hydrochloride	RBPM RH 11/1/2017	☒ Yes ☐ No *(see comments)
Any outstanding consults?	RBPM RH 11/1/2017	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☐ Yes ☐ No ☒ N/A
Are all facility inspections acceptable?	RBPM RH 11/1/2017	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	RBPM RH 11/1/2017	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☐ Yes ☐ No *(see comments) ☒ N/A
Is the final review uploaded into the current IT platform?	RBPM RH 11/1/2017	☒ Yes ☐ No

Division	Name	Date
Gloria Huang for Bing Cai	Gloria G. Huang -A Digitally signed by Gloria G. Huang -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000535685, cn=Gloria G. Huang -A Date: 2017.11.02 06:12:44 -04'00'	11/02/2017

Robert Hallenberg

Digitally signed by Robert Hallenberg
Date: 11/02/2017 06:14:25AM
GUID: 527961500009091e42f05bda047eee3b

Gloria Huang

Digitally signed by Gloria Huang
Date: 11/02/2017 12:16:21AM
GUID: 508da7000002862964eb903ad7de00fb
Comments: QE signed and approved.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 205181

INFORMATION REQUEST

Taro Pharmaceuticals U.S.A., Inc.
Attention: Kavita Srivastava
Executive Director, Regulatory Affairs
3 Skyline Drive
Hawthorne, NY 10532
kavita.srivastava@taro.com

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated February 04, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Butenafine Hydrochloride Cream, 1%.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response, no later than 7 days in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Deficencies:

Drug Substance

1. DMF# 19551 for Butenafine Hydrochloride is being reviewed (including newly submitted amendments by the DMF holder) and the DMF holder Taro Pharmaceutical Industries Ltd, will be notified of any deficiencies. We will work with the DMF holder to resolve any issues if the DMF holder responds in a timely manner. Please be aware that the quality review of the ANDA cannot be fully completed until all DMF deficiencies are adequately resolved. Therefore, additional ANDA deficiency comments may be issued based on the outcome of the DMF review. Please acknowledge this in your response.

Drug Product:

1. We note that you have separated in-process specification and DP release specification. In order to avoid any confusion, please delete the following sentence from Section 3.2.P.3.4,

control of critical steps and intermediates: *"The in-process specification for Butenafine Hydrochloride Cream, 1% is provided in Module 3.2.P.5.1 Specifications".*

2. In post-approval stability protocol (ref Section 3.2.P.8.2), you have referred to an older version of stability specification submitted in eCTD0002, 07/30/2015 (ref Section 3.2.P.8.1, stability summary and conclusion). Instead please refer to the updated DP stability specification submitted in eCTD 0003, 06/03/2016 (ref Section 3.2.P.8.1, Finished product stability specification).

B. Comment:

We expect you to comply with ICH Q3D as of January 1, 2018.

If you do not submit a complete response by May 26, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CHEMISTRY
REFERENCE # 15114065

If you have any questions, please contact Robert Hallenberg, Regulatory Business Process Manager, at (240) 402-8646 or email at robert.hallenberg@fda.hhs.gov.

Sincerely,

Robert Hallenberg, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 205181

INFORMATION REQUEST

Taro Pharmaceuticals U.S.A., Inc.
Attention: Kavita Srivastava
Executive Director, Regulatory Affairs
3 Skyline Drive
Hawthorne, NY 10532
kavita.srivastava@taro.com

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated February 04, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Butenafine Hydrochloride Cream, 1%.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days in order to continue our evaluation of your ANDA.

DMF# 19551 for Butenafine Hydrochloride is being reviewed (including newly submitted amendments by the DMF holder) and the DMF holder Taro Pharmaceutical Industries Ltd, will be notified of any deficiencies. We will work with the DMF holder to resolve any issues if the DMF holder responds in a timely manner. Please be aware that the quality review of the ANDA cannot be fully completed until all DMF deficiencies are adequately resolved. Therefore, additional ANDA deficiency comments may be issued based on the outcome of the DMF review. Please acknowledge this in your response.

List of the deficiencies:

Deficencies:

1. (b) (4)

2. (b) (4)

3.

If you do not submit a complete response by March 12, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CHEMISTRY
REFERENCE # 13098972

If you have any questions, please contact Robert Hallenberg, Regulatory Business Process Manager, at (240) 402-8646 or email at robert.hallenberg@fda.hhs.gov.

Sincerely,

Robert Hallenberg, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 205181 APPLICANT: Taro Pharmaceuticals
DRUG: Butenafine HCL Cream 1% DATE OF SUBMISSION:2-4-13

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,MaPP 5240.3 & GDUFA). At least one of the criteria must be met to receive Expedited Review Status:

1. ☐ **PUBLIC HEALTH NEED.** Events that affect the availability of a drug for which there is no alternative

2. ☐ **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - ♦ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - ♦ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. **AGENCY NEED.**
   a) ☐ Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) ☐ Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) ☐ Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) ☐ Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).
   e) ☒ MaPP 5240.3 conditions.

4. ☐ **GDUFA.** Year one and year two cohort PIV 180-day eligibility (First Generic)

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	MK/ 3-6-14
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☐ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #13

ENTER FORM INTO DAARTS DATE 3-7-14

Paste Email Copy Below:

From: West, Robert L
Sent: Thursday, March 06, 2014 12:02 PM
To: Kwong, Mandy
Subject: RE: Taro Pharmceutical's ANDA 205181 for Butenafine HCL Cream- Expedited Review Request

Yes, it appears to meet the criteria.

Bob

From: Kwong, Mandy
Sent: Thursday, March 06, 2014 11:23 AM
To: West, Robert L
Subject: Taro Pharmceutical's ANDA 205181 for Butenafine HCL Cream- Expedited Review Request

Hi Bob,

ANDA 205181, Butenafine HCL Cream, appears to be a first generic product for which there are no blocking patents or exclusivities. This is a PII patent, OTC product. RLD is Lotrimin Ultra. Should we expedite the review based on MaPP5240.3?

Orange Book OTC search for Butenafine:

Active Ingredient Search Results from "OB_OTC" table for query on "butenafine."

Displaying records 1 to 1 of 1

Appl No	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Ap
N021307	Yes	BUTENAFINE HYDROCHLORIDE	CREAM; TOPICAL	1%	LOTRIMIN ULTRA	SC

DARRTS search for Butenafine cream:

Application Search Results

TIP Click Here To Show Selected Search Criteria

Show All Rows | Export Results

	Application Type/Number	Application SubType	Product Name	Submitter	Dosage Form	Responsible Organization	Curre
View	ANDA-205181	Unknown	BUTENAFINE HYDROCHLORIDE	TARO PHARMACEUTICALS USA INC	EMULSION, CREAM	CDER/OGD	Pendin

Mandy

Mandy C Kwong, Pharm.D.
Lieutenant, U.S. Public Health Service
Regulatory Project Manager
FDA/CDER/Office of Generic Drugs
MPN1, Room 1357
7520 Standish Place
Rockville, MD 20855
240-276-8801 (office)

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/s/

MANDY C KWONG
03/07/2014

ROBERT L WEST
03/07/2014
Deputy Director, Office of Generic Drugs

M E M O R A N D U M

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

DATE : February 12, 2013

TO : Director
Division of Bioequivalence (HFD-650)

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

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 205181 for Butenafine Hydrochloride Cream, 1% (OTC) to determine if the application is substantially complete for filing.

Taro Pharmaceuticals USA Inc. has submitted ANDA 205181 for Butenafine Hydrochloride Cream, 1% (OTC). It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Taro Pharmaceuticals USA Inc. on February 4, 2013 for its Butenafine Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

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

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/s/

EDWARD WASHINGTON
02/14/2013