CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-883

Generic Name: Ammonium Lactate Cream, 12% (base)

Sponsor: Taro Pharmaceuticals USA, Inc.

Approval Date: April 10, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	X
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

APPROVAL LETTER

ANDA 75-883

APR 10 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 25, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ammonium Lactate Cream, 12% (base).

Reference is also made to your amendments dated April 11 and August 10, 2001; May 21, May 30, August 23, and October 29, 2002; and April 9, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ammonium Lactate Cream, 12% (base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lac-Hydrin® Cream, 12% (base), of Westwood Squibb Pharmaceuticals Inc.).

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

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

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

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

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

Sincerely yours,

Gary Buehler 4/10/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

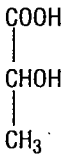
FINAL PRINTED LABELING

Ammonium Lactate Cream, 12%*

Rx only

For dermatologic use only. Not for ophthalmic, oral or intravaginal use.

DESCRIPTION: *Ammonium lactate is a formulation of 12% lactic acid neutralized with ammonium hydroxide, as ammonium lactate, with a pH of 4.4-5.4. Ammonium lactate cream also contains glyceryl monostearate, polyoxyethylene 100 stearate, polyoxyl 40 stearate, laureth-4, cetyl alcohol, light mineral oil, methylparaben, propylparaben, purified water, magnesium aluminum silicate, methylcellulose, propylene glycol, glycerin and for pH adjustment: ammonium hydroxide and lactic acid. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid and has the following structural formula:



CLINICAL PHARMACOLOGY: Lactic acid is an alpha-hydroxy acid. It is a normal constituent of tissues and blood. The alpha-hydroxy acids (and their salts) are felt to act as humectants when applied to the skin. This property may influence hydration of the stratum corneum. In addition, lactic acid, when applied to the skin, may act to decrease corneocyte cohesion. The mechanism(s) by which this is accomplished is not yet known.

An in vitro study of percutaneous absorption of ammonium lactate cream using human cadaver skin indicates that approximately 6.1% of the material was absorbed after 68 hours.

INDICATIONS AND USAGE: Ammonium lactate cream is indicated for the treatment of ichthyosis vulgaris and xerosis.

CONTRAINDICATIONS: None known.

WARNING: Use of this product should be discontinued if hypersensitivity to any of the ingredients is noted. Sun exposure (natural or artificial sunlight) to areas of the skin treated with ammonium lactate cream should be minimized or avoided (see Precautions section).

PRECAUTIONS: ***General:*** For external use only. Stinging or burning may occur when applied to skin with fissures, erosions, or that is otherwise abraded (for example, after shaving the legs). Caution is advised when used on the face because of the potential for irritation. The potential for post-inflammatory hypo- or hyperpigmentation has not been studied.

Information for Patients: Patients using ammonium lactate cream should receive the following information and instructions:

1. This medication is to be used as directed by the physician, and should not be used for any disorder other than for which it was prescribed. Caution is advised when used on the face because of the potential for irritation. It is for external use only. Avoid contact with the eyes, lips, or mucous membranes.

2. Patients should minimize or avoid use of this product on areas of the skin that may be exposed to natural or artificial sunlight, including the face. If sun exposure is unavoidable, clothing should be worn to protect the skin.

3. This medication may cause stinging or burning when applied to skin with fissures, erosions, or abrasions (for example, after shaving the legs).

4. If the skin condition worsens with treatment, the medication should be promptly discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility: **Carcinogenesis:** A long-term photocarcinogenicity study in hairless albino mice suggested that topically applied 12% ammonium lactate cream enhanced the rate of ultraviolet light-induced skin tumor formation. Although the biologic significance of these results to humans is not clear, patients should minimize or avoid use of this product on areas of the skin that may be exposed to natural or artificial sunlight, including the face. Long-term dermal carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of ammonium lactate.

Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with ammonium lactate cream. It is also not known whether ammonium lactate cream can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ammonium lactate cream should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Although lactic acid is a normal constituent of blood and tissues, it is not known to what extent this drug affects normal lactic acid levels in human milk. Because many drugs are excreted in human milk, caution should be exercised when ammonium lactate cream is administered to a nursing woman.

APR 10 2003

Pediatric Use: The safety and effectiveness of ammonium lactate cream have not been established in pediatric patients less than 12 years old. Potential systemic toxicity from percutaneous absorption has not been studied. Because of the increased surface area to body weight ratio in pediatric patients, the systemic burden of lactic acid may be increased.

ADVERSE REACTIONS: In controlled clinical trials of patients with ichthyosis vulgaris, the most frequent adverse reactions in patients treated with ammonium lactate cream were rash (including erythema and irritation) and burning/stinging. Each was reported in approximately 10-15% of patients. In addition, itching was reported in approximately 5% of patients.

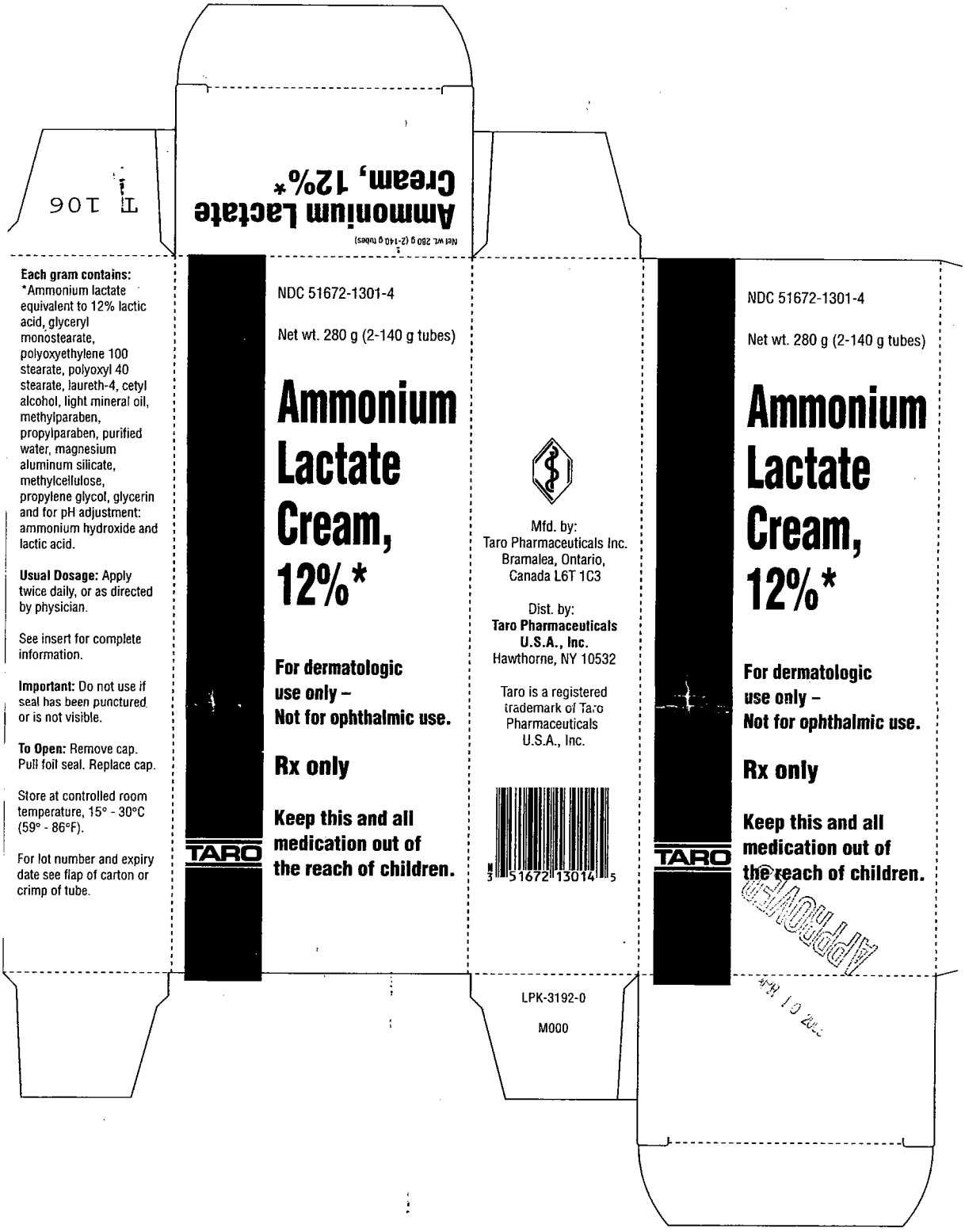
In controlled clinical trials of patients with xerosis, the most frequent adverse reactions in patients treated with ammonium lactate cream were transient burning, in about 3% of patients, stinging, dry skin and rash, each reported in approximately 2% of patients.

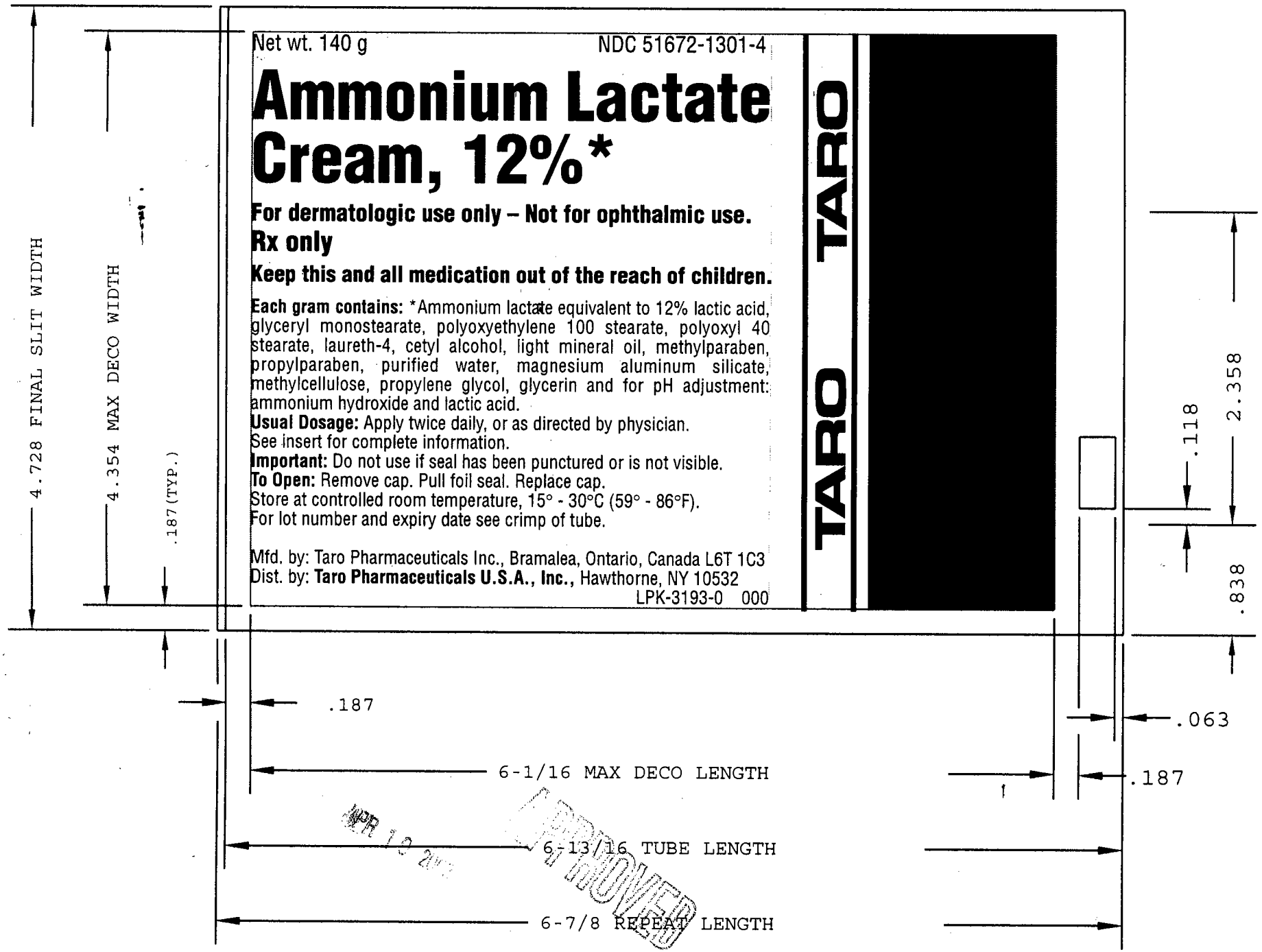
DOSAGE AND ADMINISTRATION: Apply to the affected areas and rub in thoroughly. Use twice daily or as directed by a physician.

HOW SUPPLIED: Ammonium lactate cream is available in cartons of 280 g (2-140 g plastic tubes). Store at controlled room temperature, 15°-30°C (59°-86°F).

Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3

Issued: February 2000
LPK 3194-0


Ammonium Lactate Cream, 12%*
Net wt. 280 g (2-140 g tubes)
T 106
Each gram contains:
*Ammonium lactate equivalent to 12% lactic acid, glyceryl monostearate, polyoxyethylene 100 stearate, polyoxyl 40 stearate, laureth-4, cetyl alcohol, light mineral oil, methylparaben, propylparaben, purified water, magnesium aluminum silicate, methylcellulose, propylene glycol, glycerin and for pH adjustment: ammonium hydroxide and lactic acid.
Usual Dosage: Apply twice daily, or as directed by physician.
See insert for complete information.
Important: Do not use if seal has been punctured or is not visible.
To Open: Remove cap. Pull foil seal. Replace cap.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
For lot number and expiry date see flap of carton or crimp of tube.
TARO
NDC 51672-1301-4
Net wt. 280 g (2-140 g tubes)
Ammonium Lactate Cream, 12%*
For dermatologic use only –
Not for ophthalmic use.
Rx only
Keep this and all medication out of the reach of children.
Mfd. by:
Taro Pharmaceuticals Inc.
Bramalea, Ontario,
Canada L6T 1C3
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
Taro is a registered trademark of Taro Pharmaceuticals U.S.A., Inc.
3 51672 13014 5
LPK-3192-0
M000
TARO
NDC 51672-1301-4
Net wt. 280 g (2-140 g tubes)
Ammonium Lactate Cream, 12%*
For dermatologic use only –
Not for ophthalmic use.
Rx only
Keep this and all medication out of the reach of children.
APPROVED


4.728 FINAL SLIT WIDTH
4.354 MAX DECO WIDTH
.187 (TYP.)
Net wt. 140 g
NDC 51672-1301-4
Ammonium Lactate Cream, 12%*
For dermatologic use only – Not for ophthalmic use.
Rx only
Keep this and all medication out of the reach of children.
Each gram contains: *Ammonium lactate equivalent to 12% lactic acid, glyceryl monostearate, polyoxyethylene 100 stearate, polyoxyl 40 stearate, laureth-4, cetyl alcohol, light mineral oil, methylparaben, propylparaben, purified water, magnesium aluminum silicate, methylcellulose, propylene glycol, glycerin and for pH adjustment: ammonium hydroxide and lactic acid.
Usual Dosage: Apply twice daily, or as directed by physician.
See insert for complete information.
Important: Do not use if seal has been punctured or is not visible.
To Open: Remove cap. Pull foil seal. Replace cap.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
For lot number and expiry date see crimp of tube.
Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
LPK-3193-0 000
TARO
TARO
.118
2.358
.838
.187
.063
.187
6-1/16 MAX DECO LENGTH
6-13/16 TUBE LENGTH
6-7/8 REPEAT LENGTH
APR 19 2007
APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

CSO LABELING REVIEW(S)

APPROVAL SUMMARY

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

ANDA Number: 75-883 Date of Submission: August 23, 2002 (Amendment)

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Ammonium Lactate Cream, 12%

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

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: (140 g) – Satisfactory in final print as of April 11, 2001 submission; Vol 2.1
- Carton Labeling: (2 x 140 g) – Satisfactory in final print as of April 11, 2001 submission; Vol 2.1
- Professional Package Insert Labeling - Satisfactory as of August 23, 200 submission; Vol 3.1

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Lac-Hydrin Cream 12%
- NDA Number: 20-508
- NDA Drug Name: Ammonium Lactate Cream, 12%
- NDA Firm: Bristol Myers Squibb Pharmaceutical Research, Inc.
- Date of Approval of NDA Insert: August 25, 2000
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? Yes – approved April 15, 2002
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparison
- Revisions needed post-approval: No
- Patent/Exclusivity: Refer to chart below:

Patent Data – NDA 20-508

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	None	III	None

Exclusivity-Data – NDA 20-508

Code	Reference	Expiration	Labeling Impact
M4	Changes to the Pediatric Use Section to provide information regarding safety and efficacy in pediatrics patients as young as 2 years old	Aug 25, 2003	Carved out
PED	Pediatric exclusivity	Feb 25, 2004	Carved out, replace with disclaimer replacing the text

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

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

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD: [Portions of review taken from previous review]

1. **MODEL LABELING**
   Labeling review based on the labeling for the reference listed drug (Lac Hydrin 12% Cream – Bristol Myers Squibb Pharmaceutical Research, Inc.: N 20-508/Efficacy supplement 005; approved August 25, 2000 and a labeling guidance approved April 15, 2002. The guidance approved April 15, 2002 is based on efficacy/S-005 and is a carved out version of the package insert with carved out portions protected by exclusivity and a disclaimer replacing the text regarding all protected pediatric information.

2. **CONTAINER and CARTON** – Satisfactory in final print as of April 11, 2002, Vol. 2.1

3. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARSON**
   - USP: None
   - RLD: Store at CRT, 15° to 30° C (59 to 86°F).
   - ANDA: Same as RLD.

5. **DISPENSING STATEMENT COMPARISON**
   - USP: None
   - RLD: None
   - ANDA: None

6. **PACKAGE CONFIGURATION**
   - RLD: Packaged in 140 g tubes, 2-tubes/carton and 385 g carton.
   - ANDA: Packaged in 140 g tubes, 2 tubes/carton.

   [Vol. 1.2 pg.802]

7. **CONTAINER/CLOSURE**
   Packaged in 140 g white laminate tube with a flip top closure.
   [Vol. 1.2 pg. 826]

8. **FINISHED DOSAGE FORM**
   - RLD: A white cream
   - ANDA: White to off-white, glossy, smooth cream

   [Vol. A1.2 pg. 1165]

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
   Taro Pharmaceuticals Inc.
   130 East Drive
   Bramalea, Ontario
   Canada L6t 1C3
   [Vol. A1.2 pg. 694]

Date of Review: 8/27/02 **Date of Submission: August 23, 2002**

Primary Reviewer: Bevel Weinman **Date:** 8/27/02

Team Leader: John Grace **Date:** 8/27/2002

---

cc:

ANDA: 75-883
DUP/DIVISION FILE
HFD-613/JGrace (no cc)
V:\FIRMSNZ\TARO\LTRS&REV\75883.ap.l
Review

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-883

Date of Submission: May 25, 2000 – Original submission; April 11, 2001 – Amendment.

Applicant's Name: Taro Pharmaceuticals USA, Inc.

Established Name: Ammonium Lactate Cream, 12% (Lactic Acid)

Labeling Deficiencies:

CONTAINER – Satisfactory in final print as of April 11, 2001 submission.

CARTON – Satisfactory in final print as of April 11, 2001 submission.

INSERT

1. General Comment

   Please note that Bristol-Myers Squibb has been granted a 3-year Waxman-Hatch (pediatric) exclusivity for Lac-Hydrin (ammonium lactate cream) which expires February 5, 2004.

   If your anticipated approved date is prior to February 5, 2004, then you should delete the paragraph in the "Pediatric Use" section, and replace it with the following statement:

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

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

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

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD: [Portions of review taken from previous review]

1. **MODEL LABELING**
   Labeling review based on the labeling for the reference listed drug (Lac Hydrin 12% Cream – Bristol Myers Squibb Pharmaceutical Research, Inc.: N 20-508/Efficacy supplement 005; approved August 25, 2000 and a labeling guidance approved April 15, 2002. The guidance approved April 15, 2002 is based on efficacy/S-005 and is a carved out version of the package insert with carved out portions protected by exclusivity and a disclaimer replacing the text regarding all protected pediatric information.

2. **CONTAINER and CARTON** – Satisfactory in final print as of April 11, 2002, Vol. 2.1

3. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

4. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 20-508

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	None	III	None

Exclusivity-Data – NDA 20-508

Code	Reference	Expiration	Labeling Impact
M4	Changes to the Pediatric Use Section to provide information regarding safety and efficacy in pediatrics patients as young as 2 years old	Aug 25, 2003	Carved out
PED	Pediatric exclusivity	Feb 25, 2004	Carved out, replace with disclaimer replacing the text

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - USP: None
   - RLD: Store at CRT, 15° to 30° C (59 to 86°F).
   - ANDA: Same as RLD.

6. **DISPENSING STATEMENT COMPARISON**
   - USP: None
   - RLD: None
   - ANDA: None

7. **PACKAGE CONFIGURATION**
   - RLD: Packaged in 140 g tubes, 2-tubes/carton and 385 g carton.
   - ANDA: Packaged in 140 g tubes, 2 tubes/carton.

   [Vol. 1.2 pg.802]

8. **CONTAINER/CLOSURE**

   Packaged in 140 g white laminate tube with a flip top closure.
   [Vol. 1.2 pg. 826]

9. **FINISHED DOSAGE FORM**
   - RLD: A white cream
   - ANDA: White to off-white, glossy, smooth cream

   [Vol. A1.2 pg. 1165]

10. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Taro Pharmaceuticals Inc.
130 East Drive
Bramalea, Ontario
Canada L6t 1C3
[Vol. A1.2 pg. 694]

Date of Review: 8/14/02 **Date of Submission:** May 25, 2000 – Original submission; April 11, 2001 – Amendment.

Primary Reviewer: B. Weitzman **Date:** 8/4/02

Team Leader: John Grace **Date:** 8/20/2002

cc: ANDA: 75-883
DUP/DIVISION FILE
HFD-613/Jgrace (no cc)
V:\FIRMSNZ\Taro\LTRS&REV\75883NA2.L.
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

MEDICAL OFFICER REVIEW(S)

MEDICAL OFFICER REVIEW
September 27, 2000

ANDA 75-883
Drug Product: Ammonium Lactate Cream, 12%
Sponsor: Taro Pharmaceuticals
Reference Listed Drug: Lac-Hydrin Cream, 12%, Westwood-Squibb

Background: The sponsor did not submit a protocol for review prior to conducting this study.

Title: Placebo-Controlled Bioequivalence and Efficacy Study Comparing Ammonium Lactate Cream 12% (Taro) to Lac-Hydrin ® (Westwood-Squibb) in subjects with Physician-Diagnosed Ichthyosis Vulgaris

Protocol Number: NH4 99-00

Principal Investigator: [redacted]

Study Period: Part 1 – November 8, 1999 to December 20, 1999
Part 2 – January 10, 2000 to February 29, 2000

Objectives: The objectives of this study were 1) to demonstrate the bioequivalence of ammonium lactate cream 12% manufactured by Taro Pharmaceuticals Inc. (Taro) to ammonium lactate cream 12% manufactured by Westwood-Squibb U.S.A.(Lac-Hydrin®); 2) to show superiority of Taro to placebo in the treatment of ichthyosis vulgaris; and 3) to compare the adverse event profile of the creams to establish that the creams have no unanticipated adverse effects.

Study Design: This is a two-part, randomized, double-blinded, vehicle-controlled, paired comparison, single factor trial. In Part 1, Taro and Lac-Hydrin were compared; in Part 2, Taro and placebo were compared. The lot numbers of the various treatments are listed below:

1. Taro – Ammonium lactate cream 12%, Taro Pharmaceuticals (Test drug), Lot Number S168-51851
2. Lac-Hydrin – Ammonium lactate cream 12%, Westwood-Squibb (Reference drug), Lot Number 572M061
3. Placebo – Ammonium Lactate cream placebo, Taro Pharmaceuticals, Lot Number S168-51869

Medical Officer Note: The study design is not acceptable. A simultaneous (at the same time) comparison of test, reference, and vehicle is necessary to demonstrate bioequivalence satisfactorily.

Inclusion/Exclusion Criteria:

Inclusion Criteria

a. Male or non-pregnant female.
b. Age: 18 years or older.
c. Diagnosis of ichthyosis vulgaris and scaling of 4 or greater by the 9-point scale described below.
d. Physical examination essentially within normal limits. No clinically significant underlying condition as judged by the investigator.
e. Signed informed consent after the study has been fully explained and before any procedures dictated by this protocol are performed. A parent or legal guardian must sign the consent if the subject is a minor.

Exclusion Criteria

a. Pregnancy or lactation.
b. Acute illness.
c. Superimposed infection of the area to be treated.
d. History of hypersensitivity to ammonium lactate or any of the components of the formulation.
e. Any other condition which would interfere with data interpretation or create undue risk to the subject.
f. Subjects are not to use any topical treatment for 2 weeks prior to the enrollment visit and no systemic corticosteroids within 8 weeks prior to the enrollment visit.
g. During the 42 days of the study, no treatment other than the study formulation should be used by the subjects. However, should any treatment be unavoidable during the study, an accurate record of the treatment including the name, treatment regimen, and indication must be recorded on the appropriate case report form.
h. Topical treatments to the affected areas other than the study formulations will exclude the subject from continuation in the study.

Study Procedures

Subjects were identified through advertisement or other referral to the investigator. Following screening, eligible subjects returned for the enrollment visit.

Enrollment Visit (Day 0) (Pre-Treatment)

Written informed consent was obtained. A medical history and physical was completed. Blood chemistries and complete blood count as well as a urine pregnancy test on all subjects of childbearing age.

A dermatologic exam of the two lower limbs was done in order to identify contralateral treatment sites and score them for scaling and fissuring using the following scales.

Scaling will be graded using the following 9-point scale:

0	No evidence of scaling
1	Fine scaling with limited distribution
2	Fine scaling with wide distribution, and/or many larger specks of dry skin
3	Appearance of faint, but distinct, polygonal scales with edges adherent to skin
4	Distinct polygonal scale plates with edges slightly lifted around
5	Moderate number of distinct polygonal scale plates with edges slightly lifted around circumferences of scale plates
6	Large number of distinct polygonal scale plates with edges well-lifted; may show signs of thickening and/or pigmentation around circumference of scale plates
7	Majority of area covered with thick, hyperkeratotic, pigmented scale plates
8	Involved areas completely covered with thick, hyperkeratotic, pigmented scale plates

Fissuring will be graded using the following 5-point scale:

0	No evidence of fissuring
1	Fine, limited appearance of fissuring
2	Moderate fissuring appearing between scale plates; may have light pink showing in the fissures
3	Distinct areas of fissuring between scale plates; fissures may have pink to light red appearance and/or are approximately 1/16 to ¼ inch wide
4	Severe fissuring between scale plates; fissures may have light red to deep red appearance and/or are approximately ¼ inch or more

Subjects who were eligible could be enrolled prior to receipt of the laboratory test results and would subsequently be dropped if the test results disqualified them. The two treatments were randomly assigned to each leg and the Taro study manager retained the randomization scheme. The treatments were blinded by using identical tubes and cartons for the packaging. The first application of study treatment was explained to subjects and applied at the time of enrollment. Tubes were clearly labeled for the right or left leg.

Treatment Phase – Weeks 1, 2, 3, and 4

In each part of the study, the treatment was applied twice daily for 28 days. In Part 1, the treatments applied were the Taro generic and the innovator product. Subjects were evaluated weekly by study personnel. The investigator evaluated scaling and fissuring using the scales

described above and inquired about clinical symptoms, adverse events, and concomitant medications.

Post-Treatment Phase – Weeks 5 and 6

Weekly evaluations for scaling and fissuring were done for two weeks after discontinuation of treatment.

Washout Phase

An additional 3 weeks of no treatment elapsed before the subject returned to clinic for re-evaluation for Part 2.

Part 2

The treatment phase and post-treatment phase described above were repeated.

Treatment Phase – Weeks 1, 2, 3, and 4

The treatment was applied twice daily for 28 days. Subjects applied the Taro generic and the placebo vehicle as instructed. Subjects were evaluated weekly by study personnel. The investigator evaluated scaling and fissuring using the scales described above and inquired about clinical symptoms, adverse events, and concomitant medications.

Post-Treatment Phase – Weeks 5 and 6

Weekly evaluations for scaling and fissuring were done for two weeks after discontinuation of treatment.

Study Discontinuation

Subjects could be discontinued from the study for the following reasons:

1. Pregnancy
2. Acute illness or clinically significant laboratory result
3. Significant protocol deviation
4. Serious adverse experience
5. Decision by the subject to leave for any reason

Subjects who did not complete the study and were considered non-evaluable were replaced.

Statistical Analysis

Sample Size Determination

The sample size was calculated based on ensuring confidence of 0.05, power of 0.80, an effect size of 20% or less, and a maximal coefficient of variation (CV) of 20%. A sample of 40 (80 legs) was deemed to be adequate to meet these criteria.

Non-Evaluable Patients

Subjects who did not complete the study due to treatment failure or drop out were to be considered completed subjects and would have their scores at the last visit carried over for subsequent visits. Subjects who did not complete the study due to protocol violations were to be considered protocol violations and would be excluded from the analysis.

Endpoints

The primary variable for efficacy and bioequivalence defined in the protocol was severity of scaling; fissuring data was collected (according to the protocol) for completeness.

Analysis

Each subject provided a comparison of two treatments in each part of the study. Taro vs. Westwood at multiple time points in part 1 and Taro vs. Vehicle at multiple time points in part 2. The protocol indicated that Locke's method would be used to compare the area under the response vs. time curve. The protocol stated that the data collected from this study was similar in structure to the data collected in a vasoconstrictor study, and was therefore, presumably analyzed in a similar way.

The study report stated that bioequivalence was evaluated by comparing the Taro product with the Westwood product in Part 1. The mean scaling and mean fissuring scores at each time point were used in this comparison. Using Locke's method, the criteria for bioequivalence was a 90% confidence interval around the ratio of mean AUC_T. Efficacy was demonstrated in Part 2 by comparing the Taro product to Vehicle using the mean scaling and mean fissuring scores at each time point. A sampling unit was considered to be a leg leading to 78 sampling units in this portion of the study. One way analysis of variance was used to analyze this data. Effects were considered significant if the Type III sums of squares were significant at $p<0.05$. The Kolmogorov-Smirnov test was performed on the distribution of scores from week 1-6. The distributions were considered significantly different if $p</=0.05$.

> *Medical Officer Note: The usual recommended endpoint would be either success/failure or change from baseline in scaling/fissuring scores.*

Safety Evaluation

No specific safety evaluation was described in the protocol. The study report indicates that study subjects were interviewed at the follow-up visits about any adverse events or concurrent medications.

Results

Patients Enrolled

In Part 1, 33 subjects (12 men and 21 women) were enrolled. All subjects returned for all study evaluations. In Part 2, 39 patients participated. This included the 33 subjects from Part 1 and an additional 6 patients (2 men and 4 women) who were recruited for Part 2. The study report does not explain why the sample size differs between Part 1 and Part 2.

> *Medical Officer Note: The sample size for both parts of the study is less than the sample size defined in the protocol. In addition, the sample for the "bioequivalence" study is less than that for the "efficacy" study.*

Two protocol deviations occurred: one patient was pregnant at the time of enrollment and one subject lost her medication immediately after enrollment and was re-enrolled using a different patient number. No patients were excluded due to illness, superimposed infection, hypersensitivity, adverse event, or any other condition which would (in the opinion of the study investigator) have interfered with data interpretation or created undue risk to the subject.

> *Medical Officer Note: The pregnant patient should have been excluded from the study according to the protocol.*

Baseline Demographics

The study subjects in Part 1 ranged in age from 19 to 74 (average age - 45). The majority of patients were female with 1.75 times more women enrolled than men were (21 females and 12 males). The predominant racial group represented was White (94%). Three per cent were Black and 1 patient was described as Native American. The average baseline score for scaling was 5.42 and for fissuring was 2.33. There was no difference in these scores between treatment groups at baseline.

The study subjects in Part 2 ranged in age from 19 to 74 (average age - 45). The majority of patients were female with 1.79 times more women enrolled than men were (25 females and 14 males). The predominant racial group represented was White (95%). Three per cent were Black and 1 patient was described as Native American. The average baseline score for scaling was 4.90 and for fissuring was 1.51. There was no difference in these scores between treatment groups at baseline.

Bioequivalence

The Part 1 bioequivalence data is shown in Table I. All patients were considered evaluable. Both scores in both treatment groups decreased over the four weeks of treatment and increased towards half of the Week 1 value after two weeks off treatment.

Table I
Weekly Scaling and Fissuring Scores, Part 1

	Scaling n=33		Fissuring n=33	
	Ammonium Lactate (Taro)	**Lac-Hydrin**	**Ammonium Lactate (Taro)**	**Lac-Hydrin**
	Mean+/-SD (range)	Mean+/-SD (range)	Mean+/-SD (range)	Mean+/-SD (range)
Week 0	5.42+/-1.15 (4-8)	5.42+/-1.12(4-8)	2.33+/-0.65(1-4)	2.33+/-0.65(1-4)
Week 1	2.91+/-1.35(1-6)	3.24+/-1.37(1-6)	1.39+/-0.66(0-3)	1.42+/-0.66(0-3)
Week 2	0.70+/-1.19(0-4)	0.88+/-1.22(0-4)	0.39+/-0.66(0-2)	0.45+/-0.67(0-2)
Week 3	0.30+/-0.59(0-2)	0.39+/-0.66(0-2)	0.15+/-0.36(0-1)	0.21+/-0.42(0-1)
Week 4	0.21+/-0.55(0-2)	0.21+/-0.55(0-2)	0.09+/-0.29(0-1)	0.09+/-0.29(0-1)
Week 5	1.00+/-1.17(0-4)	1.03+/-1.16(0-4)	0.36+/-0.65(0-2)	0.36+/-0.65(0-2)
Week 6	1.73+/-1.46(0-6)	1.73+/-1.46(0-6)	0.79+/-0.78(0-3)	0.79+/-0.78(0-3)

The sponsor's analysis showed no statistically significant differences between the Taro and the Westwood products for scaling at each time point ($p>0.3$). The test to reference ratio of the mean AUC_T was noted to be 93.2% (Locke's 90% confidence interval 89.7, 96.8). In addition, there were no statistically significant differences between the Taro and the Westwood products for fissuring at each time point ($p>0.7$). The test to reference ratio of the mean AUCt was noted to be 96.3% (Locke's 90% confidence interval 93.4, 99.4).

Efficacy

The Part 2 efficacy data is shown in Table II. Although no differences were noted between the Taro test product and the Vehicle product prior to initiation of this part of the study, the patients did not return to the baseline values measured prior to Part 1 after their five week washout. The Taro test product had a statistically greater effect on the reduction of both scaling and fissuring mean scores and the distribution of scores from Week 2 through Week 6.

Table II
Weekly Scaling and Fissuring Scores, Part 2

	Scaling n=39		Fissuring n=39	
	Ammonium Lactate (Taro)	**Lac-Hydrin**	**Ammonium Lactate (Taro)**	**Lac-Hydrin**
	Mean+/-SD (range)	Mean+/-SD (range)	Mean+/-SD (range)	Mean+/-SD (range)
Week 0	4.90+/-0.85 (4-7)	4.90+/-0.85(4-7)	1.51+/-0.60(1-3)	1.51+/-0.60(1-3)
Week 1	1.90+/-1.45(0-6)	2.54+/-1.55(0-6)	0.69+/-0.77(0-3)	0.97+/-0.84(0-3)

Week 2	0.95+/-1.19(0-4)	2.13+/-1.54(0-5)	0.33+/-0.62(0-2)	0.90+/-0.75(0-3)
Week 3	0.46+/-0.64(0-2)	1.38+/-1.25(0-4)	0.18+/-0.39(0-1)	0.59+/-0.64(0-2)
Week 4	0.41+/-0.68(0-2)	1.36+/-1.44(0-5)	0.10+/-0.31(0-1)	0.53+/-0.69(0-2)
Week 5	1.33+/-1.38(0-5)	2.54+/-1.62(0-6)	0.49+/-0.68(0-2)	1.00+/-0.79(0-2)
Week 6	2.33+/-1.53(0-6)	3.31+/-1.78(0-7)	0.87+/-0.73(0-2)	1.49+/-0.85(0-3)

Safety

One patient in Part 1 experienced a serious adverse event that was not related to the study drug. The pregnant patient had a spontaneous abortion on day 5 of the study. No other adverse events were reported.

Conclusion

1. The study design is not acceptable. A simultaneous (at the same time) comparison of test, reference, and vehicle is necessary to demonstrate bioequivalence satisfactorily.

2. The usual recommended endpoint would be either success/failure or change from baseline in scaling/fissuring scores

3. The sample size for both parts of the study is less than the sample size defined in the protocol. In addition, the sample for the "bioequivalence" study (which usually requires a larger sample size) is less than that for the "efficacy" study.

4. The pregnant patient should have been excluded from the study according to the protocol.

5. In order to demonstrate bioequivalence the test, reference, and vehicle products must be evaluated simultaneously. The test and reference products must be shown to be bioequivalent using 90% confidence intervals and both active products (test and reference) must be shown to be more effective than the vehicle control.

6. The sample in this study is too small to adequately assess the comparative safety of the test and reference products.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-883

3. NAME AND ADDRESS OF APPLICANT

Taro Pharmaceuticals, U.S.A. Inc.
5 Skyline Drive
Hawthorne, NY 10532

4. LEGAL BASIS FOR SUBMISSION

Taro Pharmaceutical Industries Ltd certifies that, in its opinion and to the best of their knowledge there are no patents that claim the listed drug.
Taro certifies that there are no exclusivities for the reference listed drug Lac-Hydrin cream.

5. SUPPLEMENT(s)

Original 5/25/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Ammonium Lactate

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

N/A

9. AMENDMENTS AND OTHER DATES:

7/31/00 - Telephone Amendment (Regulatory)

10. PHARMACOLOGICAL CATEGORY

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cream

14. POTENCY

12% (equivalent 12% lactic acid)

15. CHEMICAL NAME AND STRUCTURE

2-hydroxypropanoic acid.

16. RECORDS AND REPORTS

17. COMMENTS

[ ]

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 10/19/00

Supervisor: Paul Schwartz, Ph.D. 10/26/00

V:\FIRMSNZ\TARO\LTRS&REV\75-883.1.doc

Redacted _____

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

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-883

3. NAME AND ADDRESS OF APPLICANT

Taro Pharmaceuticals, U.S.A. Inc.
5 Skyline Drive
Hawthorne, NY 10532

4. LEGAL BASIS FOR SUBMISSION

Taro Pharmaceutical Industries Ltd certifies that, in its opinion and to the best of their knowledge there are no patents that claim the listed drug.
Taro certifies that there are no exclusivities for the reference listed drug Lac-Hydrin cream.

5. SUPPLEMENT(s)

Original 5/25/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Ammonium Lactate

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

N/A

9. AMENDMENTS AND OTHER DATES:

7/31/00 - Telephone Amendment (Regulatory)
3/19/01 - Minor Amendment

10. PHARMACOLOGICAL CATEGORY

Treatment of dry, scaly skin

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cream

14. POTENCY

12% (equivalent 12% lactic acid)

15. CHEMICAL NAME AND STRUCTURE

2-hydroxypropanoic acid.

16. RECORDS AND REPORTS

17. COMMENTS

Bio is deficient

The firm will be asked to tighten their limits for individual and total impurities based on their data

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 8/16/01

Acting Supervisor: Gil Kang

cc: ANDA 75-883
Division File
Field Copy

Endorsements:
HFD-623/N.Nashed/
HFD-623/G. Kang/

V:\FIRMSNZ\TARO\LTRS&REV\75-883.2.doc
F/T by: DJ 8/17/01

Redacted 10

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

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-883

3. NAME AND ADDRESS OF APPLICANT

Taro Pharmaceuticals, U.S.A. Inc.
5 Skyline Drive
Hawthorne, NY 10532

4. LEGAL BASIS FOR SUBMISSION

Taro Pharmaceutical Industries Ltd certifies that, in its opinion and to the best of their knowledge there are no patents that claim the listed drug.
Taro certifies that there are no exclusivities for the reference listed drug Lac-Hydrin cream.

5. SUPPLEMENT(s)

Original 5/25/00

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Ammonium Lactate

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

N/A

9. AMENDMENTS AND OTHER DATES:

7/31/00 - Telephone Amendment (Regulatory)
3/19/01 - Minor Amendment
4/11/01 - Labeling Amendment
8/10/01 - Bioequivalence Amendment
12/3/01 - Minor Amendment

10. PHARMACOLOGICAL CATEGORY

Treatment of dry, scaly skin

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cream

14. POTENCY

12% (equivalent 12% lactic acid)

15. CHEMICAL NAME AND STRUCTURE

2-hydroxypropanoic acid.

16. RECORDS AND REPORTS

17. COMMENTS

The firm will be asked to provide a revised drug substance certificate of analysis to include a test and results for the lactate esters.

The firm will be asked to provide all available room temperature stability data.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is deficient.

19. REVIEWER: DATE COMPLETED:

N. Nashed 3/8/02

Nashed E. Nashed, Ph.D. 3/5/02

3/9/02

Supervisor: James M. Fan 3/6/02

ANDA 75-883
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed/
HFD-627/J.Fan/
HFD-617/S.Ho/3/7/02 3/8/02

V:\FIRMSNZ\TARO\LTRS&REV\75-883.3.doc
F/T by: DJ 3/8/02

Redacted 11

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

BIOEQUIVALENCE REVIEW(S)

NOV 20 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-883 APPLICANT: Taro Pharmaceutials U.S.A. Inc.

DRUG PRODUCT: Ammonium Lactate Cream, 12%

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

1. Your proposed study design would provide an adequate test of bioequivalence and sensitivity of the test system if subjects enrolled could be simultaneously tested for all three treatments at the same time. The study design you have proposed will continue to have the problem of inter-subject variability and its effect would be more difficult to assess since the paired bioequivalence and efficacy comparisons would not be done in the same "system" or subject. In addition, the mixing of paired and parallel comparisons in the proposed analysis is problematic. A potential problem encountered in the conduct of such paired studies that administer two different treatments to two sites on the same subject is the mixing up of the treatments actually applied to each site. This would introduce additional variability.

2. The primary endpoint should be an Overall Disease Severity Scale, sometimes called Severity of Ichthyosis Vulgaris Scale, which is commonly used in treatment studies of this condition. The change in baseline of the Overall Disease Severity Scale at 6 weeks, two weeks after the end of treatment should be considered the primary endpoint for analysis. Scaling and fissuring should be considered secondary endpoints.

3. Two one-sided tests at the 0.5% level of significance should be used in the analysis. The 90% confidence interval of the difference in mean score or percent change from baseline score between the test and reference products should be within - 0.20 and + 0.20 to establish bioequivalence.

Sincerely yours,

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

CC: ANDA 75-883
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD- 600 /Mary Fanning 4/24/01
HFD- 650/Rabi Patnaik 11/5/2001
HFD-655/Nina Nwaba
HFD-650/Dale Conner 11/14/01

Insert Path and File Name(v:\firmsnz\taro\ltrs&rev\75883.def.doc)
BIOEQUIVALENCY - DEFICIENCIES Submission Date: August 10, 2001

1. **OTHER OPTIONS** (less common): Strengths: Ammonium Lactate Cream 12%

a. Bioequivalence Amendment

Outcome: **UN**

Outcome Decisions: UN (Unacceptable)

WinBio Comments

APPEARS THIS WA
ON ORIGINAL

Dates 1-1

MAR 29 2001

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-883 APPLICANT: Taro Pharmaceuticals

DRUG PRODUCT: Ammonium Lactate Cream, 12%

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

1. The study design is not acceptable. Thus, this study will not support approval of your product. A simultaneous (at the same time) comparison of test, reference, and vehicle is necessary to demonstrate bioequivalence satisfactorily.

2. The usual recommended endpoint would be either success/failure or change from baseline in scaling/fissuring scores.

3. The sample size for both parts of the study is less than the sample size defined in the protocol. In addition, the sample for the "bioequivalence" study (which usually requires a larger sample size) is less than that for the "efficacy" study.

4. The pregnant patient should have been excluded from the study according to the protocol.

5. In order to demonstrate bioequivalence the test, reference, and vehicle products must be evaluated simultaneously. The test and reference products must be shown to be bioequivalent using 90% confidence intervals and both active products (test and reference) must be shown to be more effective than the vehicle control.

6. The sample in this study is too small to adequately assess the comparative safety of the test and reference products.

Therefore for the above reasons, a new study should be submitted to support the approval of this product.

Sincerely yours,

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

CC: ANDA 75-883
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
BIO DRUG FILE

Endorsements: (Final with Dates)
HFD-600/MFanning Mary Roy 3/28/01
HFD-658/BDavit
HFD-652/KScardina
HFD-650/Dale Conner DRC 3/28/01

V:firmsnz/taro/ltrs%rev/75-883mor.doc

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 25 May 2000

1. Bio Study (STU): **UN**

Outcome Decisions:
AC - Acceptable **UN** - Unacceptable
NC - No Action **IC** - Incomplete

WinBio Comments:

The study submitted is not acceptable.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-883

CORRESPONDENCE

April 9, 2003

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

NC

re: **Ammonium Lactate Cream, 12% (Lactic Acid)**
ANDA #75-883
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ammonium Lactate Cream, 12% (Lactic Acid) submitted May 25, 2000, and to the telephone call from Ann Vu, Dr. Nashad, Jim Fan and Raman Murali of the Agency on April 9, 2003 in which the following was requested:

Comment:
Please remove the tests for [redacted] from your In-Process Specifications and add these tests to your Packaged Product Specifications.

Response:
Per the Agency's request, we have removed the tests for [redacted] from out In Process Specifications and we have added the tests for [redacted] to our Packaged Product Specifications. Attached please find a copy of the revised In Process Specification and the revised Packaged Product Specification including these changes.

This concludes our response to the Agency's telephone call of April 9, 2003.

If there are any questions regarding this application, or if additional information is required, please contact me at (914) 345-9001 x 298.

Sincerely,

4/9/03

Kalpana Rao
Vice President, Regulatory Affairs

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

October 29, 2002

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Ammonium Lactate Cream, 12% (Lactic Acid)
ANDA #75-883
Bioequivalence Amendment

ORIG AMENDMENT
N|AB
BIOAVAILABILITY

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ammonium Lactate Cream, 12% (Lactic Acid) submitted May 25, 2000, and to the telephone call between Dr. Dina Hixon (Associate Director of Medical Affairs), Carol Kim (Reviewer) and Krista Scardina of the Agency and Dan Moros, Avraham Yacobi and Kalpana Rao of Taro on October 28, 2002 in which the following was requested:

COMMENT 1:
The submission included two different patient enrollment periods. Please explain.

Response:
Per the protocol, 200 patients were to be enrolled in this study. Due to availability, patients were enrolled in two separate groups. We were able to identify 156 eligible patients by early November. Given the conditions in Montreal during the winter, these patients could not be easily maintained off all topical treatment until an additional 50 patients were identified. Furthermore, patients could not be enrolled in late November or December because the end of year holiday period would disrupt the reliability of return for follow-up visits. Therefore, our study included two different patient enrollment periods. Our first enrollment period was in early November (November 5-8) so that the six week study period would end before December 20th. After New Year's, (January 14-15) a second group of patients was enrolled, bringing us close to the 200 patients called for in the study protocol.

Comment 2:
The submission did not include any information regarding the time when the breaking of codes and unblinding occurred for these two populations.

Response:
The study blind was maintained until the second group of enrolled patients completed the study.

RECEIVED
OCT 3 0 2002
OGD / CDER

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

This concludes our response to the Agency's telephone call of October 28, 2002.

If there are any questions regarding this application, or if additional information is required, please contact me at (914) 345-9001 x 298.

Sincerely,

10/29/02

Kalpana Rao
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

H:\USERS\SUSI\WORD\ANDA\LETTERS\02sla015.doc
10/28/02 4:33 PM

August 23, 2002

TARO

Taro Pharmaceuticals U.S.A., Inc.

ORIG AMENDMENT
N/AF

Office of Generic Drugs
CDER, Food & Drug Administration, MPN II
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-883
Ammonium Lactate Cream, 12% (Lactic Acid)
Labeling Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) #75-883, submitted on May 25, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ammonium Lactate Cream, 12% (Lactic Acid). Reference is also made to the Agency's labeling deficiency letter received on August 22, 2002 in which the following was requested:

Comment:
INSERT
1. General Comment

Please note that Bristol-Meyers Squibb has been granted a 3-year Waxman-Hatch (pediatric) exclusivity for Lac-Hydrin (ammonium lactate cream) which expires February 5, 2004.

If your anticipated approved date is prior to February 5, 2004, then you should delete the paragraph in the "Pediatric Use" section, and replace it with the following statement:

[redacted]

APPEARS THIS WAY
ON ORIGINAL

RECEIVED
AUG 2 6 2002
OGD / CDER

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

Response:
We acknowledge all of the changes indicated in the August 22, 2002 labeling deficiency letter and have incorporated them into our labeling. Attached please find:

12 Final Printed Package Inserts

In addition, in accordance with 21 CFR 314.94(a)(8)(iv) we have provided a side-by-side comparison of our proposed labeling with our last submission with all of the differences annotated and explained.

This concludes our response to the Agency's labeling amendment from August 22, 2002. If you should have questions regarding this submission, please contact the undersigned, our US Agent.

Sincerely,

KRao 8/23/02

Kalpana Rao
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

MAY 30 2002

ORIG AMENDMENT
N/AB

TARO

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

Reference: **ANDA 75-883 - Ammonium Lactate Cream, 12%**
Bioequivalency Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ammonium Lactate Cream, 12% submitted July 30, 2000, the Minor (CMC) Amendments submitted March 19, 2001; December 3, 2001 and May 21, 2002 and to the bioequivalency data submitted on August 10, 2001.

Reference is also made to the Agency's "Bioequivalency Amendment" letter dated November 20, 2001 in which the following deficiencies were identified:

Comment 1
Your proposed study design would provide an adequate test of bioequivalence and sensitivity of the test system if subjects enrolled could be simultaneously tested for all three treatments at the same time. The study design you have proposed will continue to have the problem of inter-subject variability and its effect would be more difficult to assess since the paired bioequivalence and efficacy comparisons would not be done in the same "system" or subject. In addition, the mixing of paired and parallel comparisons in the proposed analysis is problematic. A potential problem encountered in the conduct of such paired studies that administer two different treatments to two sites on the same subject is the mixing up of the treatments actually applied to each site. This would introduce additional variability.

Comment 2
The primary endpoint should be Overall Disease Severity Scale, sometimes call Severity of Ichthyosis Vulgaris Scale, which is commonly used in treatment studies of this condition. The change in baseline of the Overall Disease Severity Scale at 6 weeks, two weeks after the end of treatment should be considered the primary endpoint for analysis. Scaling and fissuring should be considered secondary endpoints.

RECEIVED

JUN 03 2002

OGD / CDER

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 www.taropharma.com

Comment 3

Two one-sided tests at the 0.5% level of significance should be used in the analysis. The 90% confidence interval of the difference in mean score or percent change from baseline score between the test and reference products should be within – 0.20 and + 0.20 to establish bioequivalence.

Responses to Bioequivalence Deficiencies:

Based on the comments presented above, we have conducted a new study to establish the bioequivalence of Taro's Ammonium Lactate Cream 12% to Lac-Hydrin Cream 12%.

A copy of the report, No. NH4 0105A, which includes the following is provided in ***Attachment 5.***

1.1 A diskette containing the data
1.2 Clinical Study Report
1.3 Statistical Report
1.4 Case Report Forms
1.5 Ineligible Patients Microbiology Forms

The new clinical study has been conducted as per the guidelines stipulated in 21 CFR 320.38 and 320.63.

The above mentioned repeat bioequivalence study was conducted using a new batch of Ammonium Lactate Cream, 12% (L) S168-52994. This batch was manufactured according to the same master formula and manufacturing directions as the exhibit/biobatch of Ammonium Lactate Cream, 12% submitted in the original application, however the scale was increased to ———

In support of the new exhibit batch, we are submitting the following Chemistry, Manufacturing and Controls documentation.

Active Raw Material (Drug Substance):

1. Taro's and the ——— certificate of analysis for the drug substance, ammonium lactate, (L) 01310-R, used in the manufacture of the new biobatch **(Attachment 1).** Please note that the specifications for the drug substance remain the same as that previously submitted in the Minor Amendment of May 21, 2002.

Finished Product:

1. Executed batch records for the new ——— biobatch, (L) LS168-52994 including packaging records for the proposed marketed pack size of 140 g tubes ***(Attachment 2).*** Please note, this new biobatch was also packaged in ——— tubes and a ——— bulk holding container. The ——— tubes are not intended for distribution to the US market, and therefore only the cover page of the packaging records for this size have been included as evidence that the entire biobatch was packaged. The proposed commercial ——— batch size and process remain as submitted in the original ANDA. Finished product certificates of analysis for the in process bulk and packaged product ***(Attachment 3).***

Please note, the new biobatch was released according to specifications that were current at the time of testing. We have since revised the in process bulk product and packaged product specifications of Ammonium Lactate Cream 12% to include

[redacted] The upper limit remains at [redacted]
These changes were discussed in our Minor Amendment of May 21, 2002.

2. Three (3) months accelerated and three (3) months room temperature stability data for the new biobatch in 140 g tubes ***(Attachment 4).***

All other chemistry, manufacturing and controls information remains as presented in the original ANDA and amendments of March 19, 2001, December 3, 2001 and May 21, 2002.

This completes the Bioequivalency Amendment to the Ammonium Lactate Cream 12% ANDA. Three copies of this amendment (Review, Archive and Field) are being submitted. The Field copy contains only the Chemistry Manufacturing and Controls information included in this amendment.

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

Taro Pharmaceuticals USA, Inc.
Attn: Kalpana Rao
Vice President, Regulatory Affairs
5 Skyline Drive,
Hawthorne, NY 10532
(914) 345-9001 Ext. 298

Sincerely yours,

for K. Rao
Kalpana Rao
Vice President, Regulatory Affairs U.S.A.

/jh

ARCHIVE COPY

May 21, 2002

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place,
Room 150
Rockville, MD
20855

N/AC

ORIG AMENDMENT

Re: **ANDA #75-883 - Minor Amendment**
Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid)

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Application (ANDA) for Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid) submitted by Taro Pharmaceuticals U.S.A. Inc. on May 25, 2000 and to the amendments to the application dated August 10, 2001 and December 3, 2001. Reference is also made to the FDA's communication of March 12, 2002 in which the application was deemed deficient based on the comments presented below. The deficiencies presented represent MINOR deficiencies. For ease of review the agency's comments have been restated and are followed by Taro's response.

1. *Please provide a revised drug substance certificate of analysis to include a test and results for the* [redacted]

Response

The specifications for the drug substance have been revised to remove the [redacted], i.e. the [redacted] from the impurity specification and to list them as a separate specification. The acceptance limits for the [redacted] the known and unknown individual impurities and the total impurities remain unchanged. The revised drug substance specifications are provided in Attachment 1.

The test data for the analysis of the lot of drug substance used in the manufacture of the exhibit batch, (L) 7111-R, have been transcribed onto the most current specifications for the drug substance. The revised drug substance certificate of analysis includes the test and result for [redacted] (Attachment 2).

2. *Bioequivalency deficiencies were communicated to you on November 20, 2001 and have not been responded. Please provide a response to the bioequivalency deficiencies.*

RECEIVED
MAY 2 2 2002
OGD / CDER

5/24/02

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

Response Bio amend submitted 5/30/02. SL

Taro Pharmaceuticals U.S.A. Inc. has conducted a second bioequivalence study to establish the bioequivalence of Taro's Ammonium Lactate Cream 12% to Westwood Squibb's Lac-Hydrin Cream 12%. The final study report and responses to the bioequivalence deficiencies are forthcoming.

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

Please provide all available room temperature stability data.

Response

Provided in Attachment 3 are 24 months of room temperature (25°±2°C/60%±5% RH) stability data for Ammonium Lactate Cream, 12% (L) S168-5181, the exhibit batch used in the bioequivalence study submitted in the ANDA, and 3 months of room temperature (25°±2°C/60%±5% RH) and 3 months accelerated (40°C/75%RH) stability data for a second batch of Ammonium Lactate Cream, 12% (L) S168-52994.

Additional Information

Revised Finished Product Specifications

[redacted]

Specific Gravity Test Results for Production Batches of Ammonium Lactate Cream, 12% - 140 g Tubes

Lot	Specific Gravity
[redacted]	

observed data. The most current in process bulk product and packaged product specifications are included in **Attachment 4.**

EER noted Sam 6/19/02

Contract Testing Laboratories

At this time, Taro wishes to amend the current application to provide for the use of [redacted] in the Ammonium Lactate Cream 12% formulation. We wish to withdraw [redacted] as the [redacted] sited in the original application as performing this test. [redacted] currently performs the identification testing of [redacted] on behalf of Taro Pharmaceuticals Inc.

To support the use of [redacted], we have provided in **Attachment 5** [redacted] GMP and GDEA Certification and a brief description of services provided by this laboratory.

All other chemistry, manufacturing and controls information remains as presented in the original ANDA and amendments.

This concludes the minor amendment to the application. If there are any questions regarding this application, or if additional information is required, please contact us at:

Taro Pharmaceuticals U.S.A., Inc.,
Attn: Kalpana Rao
Vice President, Regulatory Affairs U.S.A.
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

Sincerely,

Kalpana Rao
Vice President, Regulatory Affairs U.S.A.

ARCHIVE COPY

December 3, 2001

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

ORIG AMENDMENT
N/A M

RE: **ANDA 75-883, MINOR AMENDMENT**
Ammonium Lactate Cream 12%

Dear Sir,

Reference is made to our Abbreviated New Drug Application for Ammonium Lactate Cream 12% dated May 25, 2000 and to amendments to this application dated March 19, 2001 and August 10, 2001. Reference is also made to the FDA's communication of August 21, 2001 in which the application was deemed deficient based on the comments presented below. For ease of review the agency's comments have been restated and are followed by Taro's response.

A: Deficiency:

Comment 1
Please tighten your limits for individual and total impurities based on your data for the drug substance.

Response
Taro has reviewed the current method for the determination of impurities in the drug substance, Method SOP A-1023, and we have realized that the formula used in the calculation of impurities was based on the weight of the sample and did not take into account the potency of the drug substance (as lactic acid), which is typically

We have therefore revised the analytical method SOP A-1023 to include the potency of the drug substance (as lactic acid) in the calculation of impurities. The revised method is presented in Attachment 1.

In view of the revision made to the calculation of impurities in the drug substance, we have recalculated impurity levels found in — lots of ammonium lactate (see Table 1). Please note, we had previously reported impurity levels for these lots in our Minor Amendment of March 19, 2001 which represent data uncorrected for the potency of the drug substance (as lactic acid).

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 www.taropharma.com

Redacted 2

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

Based on our recalculated data the following limits for impurities are proposed:

[redacted] NMT [redacted]
[redacted], NMT [redacted]
Any Other Individual: NMT [redacted]
Total Impurities: NMT [redacted]

The specifications for the drug substance have been revised to include these limits and the revised specification is provided in Attachment 2. No other changes were made to the specifications.

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

Comment 1
Your bioequivalence amendment of August 10, 2001 is under review.

Response
Taro acknowledges that the bioequivalence amendment of August 10, 2001 is under review.

Comment 2
The FDA District laboratory has the following comment. Please explain. The tailing factor obtained by the analyst was [redacted], neither, which is less than [redacted].

Response
The list of tailing factors for the lactic acid peak obtained during validation of Method SOP A-1023 was included in the validation report RD-MV085 (p.4). The table presented therein included values obtained during validation and initial stability testing of the ammonium lactate cream (range: [redacted]). We have now reviewed a larger body of data accumulated in recent months throughout subsequent stations in the stability program. Representative values for the tailing factor of the lactic acid peak are tabulated below:

Table 2: Tailing Factor of the Lactic Acid Peak

Date	Taro Column #	Lactic Acid Factor	Tailing
Dec. 10, 1999	289	[redacted]	
Jan. 7, 2000	289	[redacted]	
Feb. 28, 2000	307	[redacted]	
June 12, 2000	286	[redacted]	
Oct. 16, 2000	347	[redacted]	
Feb. 23, 2001	355	[redacted]	
July 3, 2001	323	[redacted]	
Sep. 11, 2001	323	[redacted]	

Redacted _____

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

This concludes the response to the agency's comments. If there are any questions in regard to this documentation, please do not hesitate to contact us at:

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

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

August 10, 2001

BIOAVAILABILITY

ORIG AMENDMENT
N/AB

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **Ammonium Lactate Cream, 12%**
ANDA #75-883
Bioequivalence Amendment

Dear Sir/Madam,

Reference is made to our Abbreviated New Drug Application submitted on May 25, 2000 under Section 505 (j) of Federal Food , Drug, and Cosmetic Act for Ammonium Lactate Cream, 12%. Reference is also made to the Agency's comments of March 29, 2001 and July 26, 2001 and also to our correspondence dated June 5, 2001.

The following is Taro's response to the Agency's comments dated March 29 and July 26 of 2001:

We will address each of the points raised in your letter dated March 29, 2001. However, we would like to present some background material and a discussion of study design, which, we hope, will reconcile our position with the letter received from the agency.

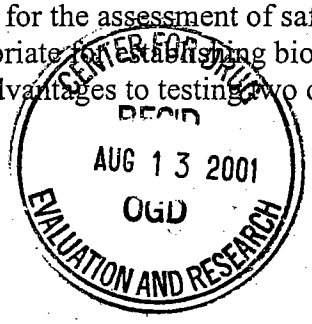
Discussion of Study Design:

I. Background

We believe that we understand and generally agree with the approach to study design for topical agents set forth in the Agency letter of March 29, 2001. Our understanding of the justification for the Agency's suggestion that group comparisons are preferred to contralateral individual comparisons is summarized as follows:

First, a drug may be absorbed and the placebo site may be influenced by drug absorption taking place at a contralateral active site. Second, if the drug is absorbed systemic safety assessment is difficult if both drug and placebo are administered to the same individual. Third, the systemic influence of the drug on various organ systems, i.e. bone marrow or liver, cannot be differentiated from the influence of disease unless treatment and placebo are studied in separate groups of patients.

In the case of topical products, study design for the assessment of safety and efficacy of a new drug may be different from a study design appropriate for establishing bioequivalence. Specifically, in bioequivalence testing there may be great advantages to testing two drugs on the same individual (e.g. the vasoconstrictor assay).



Indeed, in the case of an assessment of bioequivalence for ammonium lactate cream used to treat ichthyosis vulgaris, there are a number of factors which argue for a different approach to study design. These are:

1. The drug is not absorbed, and thus the treatment of one extremity will not influence the response observed on the contralateral extremity. The effect of ammonium lactate is exclusively local.
2. The primary safety question is usually considered to have been addressed fully by the innovator and is not ordinarily a focus of the evaluation of bioequivalence of generic drugs. This is all the more true when the test and reference vehicles are qualitatively and quantitatively similar.
3. In the case of ichthyosis, inter-individual variability is greater than contralateral variability within each individual.
4. The disease is altered by temperature and humidity conditions which amplify inter-individual variability, particularly if patients are recruited at different times and at different locations.

We believe that bioequivalence studies using a clinical/therapeutic end point should be designed to create an assay system in which the drug is the major variable. Ideally, observer variability, environmental factors and the severity and extent of the disease should be minimized or eliminated. We believe that the study design we have employed eliminates observer variability, excludes the influence of environmental factors such as season, temperature, humidity, diet, etc. and minimizes the influence of the severity and extent of disease. Since ammonium lactate cream is not absorbed, and the effect is almost exclusively local, treatment applied to one extremity should not influence the outcome on the contralateral extremity and vice-versa. We believe that safety issues have been dealt with by the innovator in the NDA and should not be a primary issue in a bioequivalence study.

We would like to review the results of our study in the following paragraphs.

II. Bioequivalence of Ammonium Lactate Cream Products:

Ichthyosis is prominently influenced by environmental factors, most significantly the low humidity of indoor areas in winter. In our bioequivalence study, in order to reduce variability of response of patients, it was desirable to treat all individuals at approximately the same time of year, and if possible, at the same general location.

To achieve this goal, we recruited a population of 30 to 40 patients with ichthyosis vulgaris from the greater Montreal region. Patients were treated with a two phase study design. The first phase was a double blind bioequivalence study in which patients were treated with a Taro and Reference Listed Drug, randomized to either inferior extremity. Thus, a paired comparison of the degree of improvement in response to treatment could be made similar to the comparison of degree of blanching in a vasoconstrictor test. The time points chosen were a weekly assessment of both scaling and fissuring using the same scales (5 point and 9 point, respectively) employed in studies for the original NDA as found in the summary basis of approval.

Following the bioequivalence phase, and after a four week wash out period, the same patient population (assay system) was tested to demonstrate that it could distinguish differences between Test and Reference Listed Products adequately. The second phase was a double blind efficacy study in which each patient was treated with the active Taro Product and the Taro vehicle randomized to either inferior extremity. Again, a comparison of degree of improvement in response to treatment could be made using the same study format and grading system described above. Furthermore, this phase provided additional safety data on the Taro product without a potential bias.

The sequence bioequivalence assay first (test vs. reference) and assay validation study second, (test vs. placebo) was chosen to eliminate any confounding variability produced by a prior treatment. Thus, to the extent that any remaining attenuation of disease as a result of therapy in the first phase was still present in the second phase, the differentiation of Taro active from Taro vehicle was made more difficult. Thus, the assay validation would be even more certain. To reverse the order (i.e. efficacy first and bioequivalence second) could potentially raise questions about a different response between prior treated and prior untreated legs.

The assay validation phase (efficacy study) was particularly demanding since the data demonstrate that the vehicle has a beneficial effect on the symptomatic state. The results demonstrate adequate sensitivity of the assay system to distinguish between the Taro Ammonium Lactate Cream, 12% Formulation and an Active Control with a significance of $p<.01$. Additionally, comparison of data from both Phase I and Phase II clearly demonstrates that both Test and Reference Listed products are significantly superior to the placebo (Taro vehicle).

III. Demonstration of an environmental impact;

Because of our experimental design, we are able to compare the response of 32 patients using the Taro Ammonium Lactate Cream under different environmental conditions by comparing the treatment responses in the first phase to the treatment responses in the second phase.

The first phase was conducted in Montreal in November 1999. The second phase was conducted under somewhat harsher weather conditions in late January and February 2000. Patients in the second phase had a slightly lower symptom score on entry than in the first phase **(See Attachment – Table 1)**. However, after four weeks of treatment patients in the second phase, during harsher weather, had a lower cure rate of 66% as opposed to 84% in the first phase **(See Attachment – Table 2 p=0.08).** For purposes of this evaluation we define "cure" as a zero grade for scaling and fissuring. Thus, the same patients treated with the same material for the same duration of time and evaluated by the same examiner looked different depending on the overall environmental condition.

We believe that this data supports our view that in a bioequivalence study utilizing patients with ichthyosis vulgaris, where we want the difference in formulation to be the only significant variable, it is valuable to enter all patients at the same time, in the same place, and to evaluate them under the same conditions. This approach will result in minimum variability in response and would need a relatively smaller group to establish bioequivalence in patients.

IV. Evaluation Based on the Definition of Cure

We agree that an evaluation after four weeks of treatment can be based on a definition of cure and we are providing such a comparison between the ammonium lactate cream products of Taro and Bristol Myers Squibb using as the definition of cure a grade of zero for scaling and fissuring (i.e. 0,0). The Taro and Bristol Myers Squibb products are bioequivalent employing this definition **(See Attachment - Table 4),** as well as under a definition of cure that permit a scoring of 1,0 or 0,1 or 1,1. However, we still need a graded evaluation of relapse at two weeks, since one hundred percent of patients re-develop signs and symptoms after two weeks off treatment. Thus, while this treatment offers valuable relief of symptoms and dramatic improvement in signs, it does not offer even a short-term "cure". After two weeks off therapy, it is important to assess whether the rate of return of signs is similar in the two groups of patients. Therefore, we believe we need a comparison of signs of the disease at six weeks in order to evaluate relapse.

In our study the of signs of disease score after two weeks without treatment was identical when comparing the Taro and Bristol Myers Squibb products and was significantly different when the Taro product is compared to the Taro vehicle alone.

V. Response to Specific FDA Comments:

In the light of the above, we would like to respond to each point raised by the agency. Our response will address comments #1 and #5 together.

Comment #1:
The study design is not acceptable. Thus, this study will not support approval of your product. A simultaneous (at the same time) comparison of test, reference, and vehicle is necessary to demonstrate bioequivalence satisfactorily.

Comment #5:
In order to demonstrate bioequivalence the test, reference, and vehicle products must be evaluated simultaneously. The test and reference products must be shown to be bioequivalent using 90% confidence intervals and both active products (test and reference) must be shown to be more effective than the vehicle control.

Response 1 & 5:
Taro proposes to assess specifically the study design for ammonium lactate as conducted in this study. Although the Taro vehicle and reference products were not given simultaneously under the conditions of this study and by this protocol, we believe that comparison of reference and vehicle can reasonably be made.

The study design and its rationale are described above. The guiding principle behind the design is the need for simultaneous comparisons in assessing the response to treatment in the setting of ichthyosis vulgaris.

In Phase II of the study (efficacy testing of test of vehicles) 33 of 39 patients also received the reference in Phase I of the study. While this comparison of references to the test vehicle (Taro product) was not conducted simultaneously, it was done in the same patients. The only variable may be the timing of the study. We believe that under the conditions of this study, the strong difference between the response to the reference and to the test vehicle ($P<0.001$) in the same patients (not parallel groups) clearly points to the efficacy of the reference. All statistical tests show that bioequivalence and efficacy with 90% confidence interval using the two, one-sided test procedures. There is no clear guidance or indications that for a product such as ammonium lactate with local effects only that this comparison may be unreasonable or inconclusive.

In conclusion, we believe that the study demonstrates and proves bioequivalence between test and reference and confirms the efficacy of both tests and references. (See Attachment I - Table 3.)

Comment #2:
The usual recommended endpoint would be either success/failure or change from baseline in scaling/fissuring scores.

Response 2:
We have reanalyzed the data from our study, using either complete success (clearing) or change from baseline observation. The data support bioequivalence of the test and reference products using as a definition of success either a score of 0,0, [complete clearing] or a 0,1, 1,0 or 1,1 scaling/fissuring score. (See Attachment I – Table 4)

Comment #3:
The sample size for both parts of the study is less than the sample size defined in the protocol. In addition, the sample for the "bioequivalence study (which usually requires a larger sample size) is less than that for the "efficacy" study.

Response 3:
The primary goal of the study design was to enter the entire patient population at a single site and at a single point in time. We chose the number 40 because we believed that by using multiple point observation and the Locke's method of statistical analysis should provide sufficient statistical power to detect bioequivalence between two products. (See Attached – Table 5). Also we believed that this was the maximum number of patients that we could reasonably expect to recruit at one site and at one time.

Only 33 patients could be recruited for stage one. We believed that this number of patients would be adequate for the study, under the conditions of the study and the protocol design. Thus we initiated drug administration in early November in order to finish the 6-week study before the holiday season began. An additional group of 6 patients became available after the holidays and were utilized in the efficacy phase of the study. However, even if those 6 patients are excluded to keep the patient set identical in both phases of the study, the efficacy phase clearly achieves statistical significance. The protocol allowed for

enrollment of 40 patients in either phase of the study, thus the decision was made to run the study with the additional six patients. No protocol amendments were deemed necessary.

Comment #3:
In addition, the sample for the "bioequivalence study" (which usually requires a larger sample size) is less than that for the "efficacy" study.

Response #3:
We agree that a larger sample size is usually required to establish bioequivalence than simply demonstrate difference from placebo. Indeed, with our study design, we are able to demonstrate efficacy with fewer than 33 patients. As called for in the protocol we attempted to find and enroll as close to 40 patients as possible. However, with the unique study design and appropriate statistical analysis, sufficient power was attained to meeting 90% confidence internal, using the two one-sided test procedure.
Also, the nature of ichthyosis is such that drug treatment improvement in the disease condition can be readily detected and that clinical observation can be reliably assessed/measured at appropriate season of the year, i.e. the coldest and the driest.

Comment #4:
The pregnant patient should have been excluded from the study according to the protocol.

Response #4:
We agree with the reviewer's observation and re-analyzed the data excluding this patient. The elimination of this patient from the data set does not change the statistical outcome. (See Attachment I - Table 6)

Comment #6:
The sample in this study is too small to adequately assess the comparative safety of the test and reference products.

Response #6:
It is our understanding that safety concerns have been addressed already by the innovator and that our primary goal is to establish bioequivalence. While this is always the case for an oral dosage form product, it is also the case for a semisolid topical products which consist of active and inactive ingredients in quantities which are allowed by the FDA. For example, most corticosteroid products demonstrate bioequivalence through vasoconstrictor studies conducted with less than 40 patients and require no additional safety testing in pursuit of an ANDA. In this study, a total of 39 patients received the test and the test vehicle simultaneously (Phase II of the study) for 28 days. There were few, if any, adverse reactions attributable to the active or inactive ingredients, confirming safety of Taro's ammonium lactate cream product. (See Attachment I – Table 7)

In accordance with the Agency's wishes, Taro proposes to conduct an additional study with Taro's vehicle and the reference listed product to show that the active drug is indeed superior to

the vehicle. We believe that this will provide further support for the bioequivalence of our product to the reference listed drug.

To complete the bioequivalence evaluation of ammonium lactate cream and to meet the Agency's concern about the comparison of the reference listed drug to Taro's vehicle, we propose to conduct a two-arm study with reference listed drug and Taro vehicle in 30 – 40 patients using the same design as we employed to establish bioequivalence between Taro and reference listed drug and compare Taro product to vehicle. This should conclusively complete our tests and meet the Agency's requirement regarding the bioequivalence of Taro and the reference listed product. We appeal to the Agency to consider this additional study.

[

]

Should the Agency consider our proposal given above insufficient, Taro will proceed to conduct a new study to compare the Taro Product, the reference listed drug and Taro vehicle simultaneously. Based on the rationale given above, we believe that Taro should pursue a modified parallel design study in which the three products should be given to patients in a randomized fashion allowing the use of each inferior extremity for a different product and not confining one product to one patient. The study proposed in this paragraph meets all of the Agency's requirements with a single exception that we suggest to use both extremities for both products according to randomized design. As noted above and based on our clinical experiences with ammonium lactate products, this design will reduce variability and will increase the sensitivity of the assay for ammonium lactate cream. Please see the attached protocol for your review. (See Attachment III).

Taro would like to request the Agency to consider and to comment on both proposals. We believe that for ammonium lactate cream the approach of modified parallel design study offers more conclusive results, particularly, when every time point as well as the combination of the five points (AUC) are statistically evaluated.

We have requested to meet with the Agency to discuss the study design and to review the merit of Taro's proposed approach. We hope that the Agency will consider our appeal and permit us to conduct a study particular scientifically sound.

This concludes our response to the Agency's letter of March 29, 2001 and July 26, 2001. If you should have any questions, please contact the undersigned.

Sincerely,

8/10/01

Kalpana Rao

Vice President, Regulatory Affairs, USA

April 11, 2001

TARO

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

ORIG AMENDMENT
NIAF

Reference: **ANDA #75-883**
Ammonium Lactate Cream, 12% (Lactic Acid)
Labeling Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on May 25, 2000 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Ammonium Lactate Cream, 12%. Reference is also made to the letter received from the Agency on April 6, 2001 in which the following Labeling Deficiencies were noted:

1. *CONTAINER (140 g) - Satisfactory in draft*
2. *CARTON (2 x 140 g) - Satisfactory in draft*
3. *INSERT - Satisfactory in draft*

Please submit your labels and labeling in final print.

Response:
Attached please find:

12 Final printed 140 g tube labels
12 Final printed 2 x 140 g carton labels
12 Final printed package inserts

This concludes our response to the Agency letter of April 6, 2001. If you should have any questions, please contact the undersigned.

CENTER FOR DRUG
RECD
APR 12 2001
OGD
EVALUATION AND RESEARCH

Sincerely,

4/11/01

Kalpana Rao
Director, Regulatory Affairs

01sla007

March 19, 2001

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

RE: ANDA: 75-883 - Minor Amendment
Ammonium Lactate Cream, 12%

Dear Sir,

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

A. Deficiencies

1. Please revise your drug substance specifications to include limits and specifications for specific rotation, individual (known and unknown) and total impurities, assay and ratio and provide data.

Response

As requested, the specification for the drug substance has been revised to include limits and specifications for specific rotation, individual known and unknown impurities, total impurities, assay and ratio. The revised specification is provided in Attachment 1.

Eleven (11) lots of the were analysed for assay and results for these parameters as well as the derived ratio have been tabulated below.

3/23/01

Redacted 2

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

Based on this data the following limits have been proposed:

[redacted] NMT [redacted]
Total [redacted] NMT [redacted]
Any Other Individual: NMT [redacted]
Total Impurities: NMT [redacted]

Of the [redacted] lots of the drug substance analysed, [redacted] was not detected in [redacted] of them; because of the low levels of [redacted], levels of this impurity will be included with "Any Other Individual" impurities.

2. Please provide limits and specifications for homogeneity and viscosity for in-process controls.

Response
Limits and specifications for homogeneity and viscosity for in process controls have been established and the revised in process specification is provided in Attachment 4.

3. Please revise your specification for finished drug product to include limits and specifications for homogeneity, specific gravity, viscosity and degradation products.

Response
The finished drug product release specification has been revised to include limits and specifications for homogeneity, specific gravity, viscosity and degradation products. The revised specification is provided in Attachment 5.

Please note that [redacted] a synthetic impurity, was removed from the individual and total degradation product quantitation of the cream. Its level is controlled and reported in the drug substance. The calculation section of Method SOP A-1023 has been revised. The revised method is also provided in Attachment 5.

4. Please revise stability specifications to include limits and specifications for homogeneity, specific gravity, total [redacted], viscosity, and degradation products.

Response
The stability specification has been revised to include limits and specifications for homogeneity, total [redacted], viscosity and degradation products. The revised specification is included in Attachment 6.

A specification and limit for specific gravity has not been included. Our rationale is that specific gravity does not change with time for a cream packaged in an impermeable sealed [redacted] laminate tube.

5. [redacted]

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

1. The firm referenced in your application should be in compliance with CGMP at the time of the approval.

Response
Taro Pharmaceuticals U.S.A. Inc. acknowledges that the firms referenced in the application should be in compliance with CGMP at the time of approval.

2. Your bioequivalence study is under review.

Response
Taro Pharmaceuticals U.S.A. Inc. acknowledges that the bioequivalence study is under review.

3. Your analytical methods have been submitted to FDA district laboratories for validation. Please submit samples promptly when so requested.

Response
Taro Pharmaceuticals U.S.A. Inc. acknowledges that the analytical methods have been submitted to the FDA district laboratories for validation. Samples were submitted to the NorthEast Regional Laboratory on November 9, 2000.

4. Please provide all available room temperature stability data.

Response
18-Months of room temperature stability data for the test batch (L) S168-51851 is included in Attachment 7.

This concludes the amendment to this application. Should you have additional concerns please contact us at:

Taro Pharmaceuticals U.S.A. Inc.
ATT. Kalpana Rao
Director, Regulatory Affairs
5 Skyline Drive,
Hawthorne, New York 10532
Tel: (914) 345-9001 Fax: (914) 593-0078

Sincerely yours,

TARO PHARMACEUTICALS INC.

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

/jh

APPEARS THIS WAY
ON ORIGINAL

July 31, 2000

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

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

NEW CORRESP
NC

Reference: ANDA #75-883
Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid)
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on May 25, 2000 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Ammonium Lactate Cream 12% (equivalent to 12% lactic acid). Reference is also made to a phone call on July 14, 2000 from Paras Patel of the Agency and to our response which was faxed on July 21, 2000.

The following information was requested:

- FDA form 356h with the original signature;
- Patent Certification with the original signature;
- Financial Certification statements with the original signature;
- cGMP Certification from the contract facility ——————— with the original signature.

Please note that all of the above requested items are included herein. This concludes our response to the Agency phone call of July 14, 2000

If you should have any questions, please contact the undersigned.

Sincerely,

Kal 7/31/00

Kalpana Rao
Director, Regulatory Affairs

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

ANDA 75-883

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

JUL 21 2000

Dear Madam:

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

Reference is also made to the telephone conversation dated July 14, 2000 and to your correspondence dated July 21, 2000.

NAME OF DRUG: Ammonium Lactate Cream, EQ 12% Base

DATE OF APPLICATION: May 25, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 26, 2000

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

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

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5849

Sincerely yours,

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

Taro Pharmaceuticals U S.A., Inc.

July 21, 2000

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

NEW CORRESP
NC

Re: **Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid)**
ANDA# 75-883
Telephone Amendment

Dear Mr. Buehler:

Reference is made to the above referenced ANDA which was submitted on May 25, 2000. Reference is also made to the teleconference on July 14, 2000 between Paras Patel of FDA and
myself (Kalpana Rao).

As per discussion I am faxing the following requested information:

1. 356H form with original signature.
2. Patent Certification with original signature.
3. Financial Certification Statements with original signatures.

We are still waiting to receive the original cGMP certification from the contract facility, _____. We expect to receive it some time early next week.

Therefore, we commit to send via fed-ex, all the above mentioned originals as soon as we receive the last original document.

Please contact me at (914) 345-9001 Ext. 298 should you need any additional information.

Sincerely,
TARO PHARMACEUTICALS INC.
Kalpana Rao 7/21/00

Kalpana Rao
Director, Regulatory Affairs, USA

75-883

TARO

Taro Pharmaceuticals Inc.

May 25, 2000

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

Re: **Original Abbreviated New Drug Application (ANDA) for Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid)**

This application also includes a CMC electronic submission ESD.

Dear Mr. Sporn:

Taro Pharmaceuticals U.S.A. Inc. submits today an original Abbreviated New Drug Application (ANDA) seeking approval to market Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid) that is bioequivalent to the listed drug, Lac-Hydrin®12% (ammonium lactate) Cream, manufactured by Westwood-Squibb Pharmaceuticals Inc. pursuant to NDA 020508001.

This ANDA consists of 2 volumes. Taro Pharmaceuticals U.S.A. Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and two (2) technical review copies (in red folders) which contain all the information in the archival copy with the exception of the Bioequivalence Section (VI). A separate copy of the Bioequivalence Section is provided in orange folders.

This application also includes a CMC electronic submission ESD. The electronic files have been provided in duplicate on 3.5" virus-free diskettes in the archival copy of the ANDA (blue jackets). The information provided in these files is identical to the hard copy ANDA submission.

Also provided in this application, are electronic data files for the clinical study, Protocol NH4 9900. The files are provided on a 3.5" virus-free diskette in the bioequivalence copy of the ANDA (orange jackets).

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 26 2000
OGD

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

Original Abbreviated New Drug Application (ANDA)
Ammonium Lactate Cream, 12% (equivalent to 12% lactic acid)

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

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

Sincerely,
TARO PHARMACEUTICALS INC.

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

/J. Hobbs, B.Sc.

Enclosures:

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