

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202736Orig1s000**

**OTHER REVIEW(S)**

## SEALD Director Sign-Off Memo and Labeling Review

<b>Product Trade Name (Non-Propriety Name)</b>	<b>SKLICE (ivermectin) lotion, 0.5%, for topical use</b>
Application Number/Supplement Number	NDA 202736
Type of Application	Original Submission
Indication	Treatment of head lice infestation in patients 6 months of age and older
Applicant	Topaz Pharmaceuticals, Inc.
Office/Division	ODE III/DDDP
Division Project Manager	Dawn Williams, BSN
Submission Date	April 7, 2011
PDUFA Goal Date	February 7, 2012
SEALD Review Date	February 1, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RPh, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

# SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

# SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**
  - A horizontal line must separate the TOC and FPI.
  - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
  - For Pregnancy Category X drugs, list pregnancy as a contraindication.
  
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
  - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
  - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
  
- **Use in Specific Populations**
  - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.
  
- **Patient Counseling Information**
  - This section is required and cannot be omitted.
  - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
    - “See FDA-approved patient labeling (Medication Guide)”
    - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
    - “See FDA-approved patient labeling (Patient Information)”
    - “See FDA-approved patient labeling (Instructions for Use)”
    - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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JEANNE M DELASKO  
02/01/2012

LAURIE B BURKE  
02/02/2012

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Products

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

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**Date:** December 5, 2011

**To:** Dawn Williams, DDDP

**From:** Lynn Panholzer, PharmD, OPDP, Division of Prescription Drug Promotion  
Sheetal Patel, PharmD, OPDP, Division of Direct-To-Consumer Promotion

**Re:** NDA# 202736  
Sklice (ivermectin) Lotion 0.5%

As requested in your consult dated July 12, 2011, OPDP has reviewed the draft labeling (package insert [PI], patient package insert [PPI], and carton/container labeling) for Sklice (ivermectin) Lotion 0.5%. OPDP's comments are based on the proposed, substantially complete, marked-up version of the PI and PPI sent to OPDP by DDDP via e-mail on November 15, 2011, and on the carton/container labeling submitted by the applicant on October 11, 2011. We note that, per DDDP's November 15, 2011 email, the dosage form for this product will be "lotion" and not "cream" and the PI will be changed accordingly.

OPDP's comments on the PI and PPI are provided directly in the attached, marked-up copy of the labeling. We have the following comment on the carton/container labels:

1. The order of the inactive ingredients listed on the tube and box labels is different than the order of the inactive ingredients listed in the draft PI. Is this acceptable?

If you have any questions about OPDP's comments on the PI or carton/container labeling, please contact Lynn Panholzer at 6-0616 or at [Lynn.Panholzer@fda.hhs.gov](mailto:Lynn.Panholzer@fda.hhs.gov). If you have any questions about our comments on the PPI, please contact Sheetal Patel at 6-5167 or at [Sheetal.Patel@fda.hhs.gov](mailto:Sheetal.Patel@fda.hhs.gov).

15 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/  
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LYNN M PANHOLZER  
12/05/2011

SHEETAL PATEL  
12/05/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: December 2, 2011

To: Susan J. Walker, MD, Director  
**Division Dermatology and Dental Products (DDDP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Team Leader, Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling Reviewer  
**Division of Medical Policy Programs**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs**

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): Sklice (ivermectin)

Dosage Form and Route: Topical Cream, 0.5%

Application Type/Number: NDA 202736

Applicant: Topaz Pharmaceuticals Inc.

OSE RCM #: 2011-3365

## 1 INTRODUCTION

This review is written in response to a request by the Division Dermatology and Dental Products (DDDP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert for Sklice (ivermectin) Topical Cream, 0.5%.

On April 7, 2011, Topaz Pharmaceuticals Incorporated submitted original New Drug Application (NDA) 202736 for Sklice (ivermectin) Topical Cream, 0.5% with the proposed indication for the topical treatment of head lice (b)(4) in patients 6 months of age and older.

## 2 MATERIAL REVIEWED

- Draft Sklice (ivermectin) Topical Cream, 0.5% Patient Package Insert (PPI) received on April 7, 2011 and revised by the review division throughout the current review cycle and received by DMPP on November 28, 2011.
- Draft Sklice (ivermectin) Topical Cream, 0.5% Prescribing Information (PI) received April 7, 2011, and revised by the review division throughout the current review cycle and received by DMPP on November 28, 2011.
- Approved Natroba (spinosad) topical suspension, 0.9% comparator labeling dated January 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is consistent with the approved comparator labeling where applicable.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

## **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

14 pages of draft labeling has been withheld in full as  
B(4) CCI/TS immediately following this page

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/s/  
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LATONIA M FORD  
12/02/2011

BARBARA A FULLER  
12/02/2011

LASHAWN M GRIFFITHS  
12/05/2011

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: November 11, 2011

TO: Dawn Williams, Regulatory Project Manager  
Jane Liedtka, M.D., Medical Officer  
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Team Leader (Acting)  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Division Director (Acting)  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 202736

APPLICANT: Topaz Pharmaceuticals, Inc.

DRUG: Sklice<sup>®</sup> (0.5% ivermectin cream)

NME: No

THERAPEUTIC  
CLASSIFICATION: Standard Review

INDICATION: Treatment of head lice (b)(4) in patients 6 months of age and older

CONSULTATION REQUEST DATE: May 20, 2011

DIVISION ACTION GOAL DATE: January 25, 2011

PDUFA DATE: February 7, 2012

**I. BACKGROUND:**

The Applicant submitted this NDA for the use of Sklice<sup>®</sup> to support an indication for the treatment of head lice <sup>(b) (4)</sup> in patients 6 months of age and older. There were two studies, Protocols TOP011 and TOP012, both entitled "A Double-blind Randomized Study to Compare the Efficacy, Safety and Local Tolerability of a 0.5% Ivermectin Cream Compared to a Topical Vehicle Control in Subjects with *Pediculus Humanus Capitis* Infestation" submitted in support of the indication.

The conduct of Protocols TOP011 and TOP012 was inspected. Both protocols were double-blind, randomized, vehicle-controlled, two-arm studies to determine the safety and efficacy of the test article in the treatment of head lice and ova in patients six months of age and older.

The primary efficacy parameter was the proportion within each treatment group of index subjects who were lice free (without live lice) on Day 15.

The four Clinical Investigator (CI) sites were selected on the basis of high enrollment. In addition, large differences in treatment response between active and control arms were noted at Dr. Perry’s site for Protocol TOP011 and at Ms. Shepherd’s site for Protocol TOP12.

**II. RESULTS (by Site):**

<b>Name of CI, Location</b>	<b>Protocol #/ # of Subjects/</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Patti J. Perry, M.D. 1832 South 8th Avenue Yuma, AZ 85364-5517	TOP011/ 20/	25-28 Jul 11	NAI
Katherine R. Shepherd 604 Gallatin Avenue Suite 108 Nashville, TN 37206-3489	TOP012/ 24/	26-29 Jul 11	NAI
Kirk D. Coverston, M.D. 888 N. Alta Avenue Dinuba, CA 93618-3001	TOP011/ 24/	12-15 Aug 11	NAI
Rosmeri Montalvo 6758 North Military Trail, Suite 110 West Palm Beach, FL 33407	TOP011/ 24/	8-11 Aug 11	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. **Patti J. Perry, M.D.**

1832 South 8th Avenue  
Yuma, AZ 85364-5517

- a. **What was inspected:** At this site, 53 subjects were enrolled. The records of 46 subjects were reviewed. The records reviewed included, but were not limited to, informed consent, financial disclosure, training, screening/enrollment, adverse events, primary efficacy data, sponsor/CRO/IRB correspondence, and test article accountability and storage.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. The inspection did note that Subjects 205-01 and 205-02 were dispensed tubes of the test article weighing 178 grams instead of the usual 134 grams, a difference of approximately 44 grams. During the inspection, no explanation for this value was given and it could not be determined whether these tubes actually contained more of the test article or whether it was a weighing error. The significance of this finding is not known and was discussed with the review division. It is noted that the tubes of test article were weighed before and after use and that the amount used varied from approximately 44 to 98 grams, a difference of 54 grams. The review division may wish to consider the impact, if any, of the data generated for Subjects 205-01 and 205-02 on the overall safety and efficacy conclusions reached in review of the NDA.
- c. **Assessment of data integrity:** Other than the issue noted above, the study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

2. **Katherine R. Shepherd**

604 Gallatin Avenue, Suite 108  
Nashville, TN 37206-3489

- a. **What was inspected:** At this site, 97 subjects were screened and 58 subjects were enrolled. The records of all of the subjects were reviewed. Records reviewed included, but were not limited to, all informed consent forms, IRB and sponsor correspondence, test article accountability, financial disclosure, and training records. Source documents were compared with data listings.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

3. **Kirk D. Coverston, M.D.**

888 N. Alta Avenue  
Dinuba, CA 93618-3001

- a. **What was inspected:** At this site, 102 subjects were screened and 73 were enrolled and completed the study. The records of 38 subjects were reviewed. Records reviewed included, but were not limited to, informed consent, inclusion/exclusion criteria, primary efficacy data, sponsor/CRO/IRB correspondence, drug accountability and storage, protocol deviations, financial disclosure, and study training.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

4. **Rosmeri Montalvo**

6758 North Military Trail, Suite 110  
West Palm Beach, FL 33407

- a. **What was inspected:** At this site, 92 subjects were screened, 72 were enrolled, and 71 completed the study. The records of 39 subjects were reviewed. Records reviewed included, but were not limited to, all informed consent forms, medical histories, inclusion/exclusion criteria, treatment success, drug accountability and storage, concomitant medications, and sponsor, monitor, IRB, and site correspondence. Source documents were compared with data listings.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

The clinical investigator sites of Drs. Perry and Coverston, and Ms. Shepherd and Ms. Montalvo were inspected in support of this NDA. None of these clinical sites were issued a Form FDA 483. No regulatory violations were noted at any of these sites; however, at Dr. Perry's site, it was noted that two subjects were treated with test article from tubes that weighed substantially more than the other tubes of test article. The significance of this finding is unknown but it was discussed with the review division. The review division may wish to consider the impact, if any, of the data generated for these two subjects on the overall safety and efficacy conclusions reached in review of the NDA. Other than consideration of the issue noted immediately above at Dr. Perry's site, the studies at these four clinical sites appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Team Leader (Acting)  
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Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit -Sheth, M.D.  
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Office of Scientific Investigations

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/s/  
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ROY A BLAY  
11/14/2011

SUSAN LEIBENHAUT  
11/14/2011

TEJASHRI S PUROHIT-SHETH  
11/14/2011



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**ADDENDUM TO PEDIATRIC AND MATERNAL HEALTH STAFF REVIEW**

**Date:** November 7, 2011

**From:** Elizabeth L. Durmowicz, MD, Medical Officer

**Through:** Hari Cheryl Sachs, MD, Team Leader  
Lisa Mathis, MD, OND Associate Director  
Pediatric and Maternal Health Staff, Office of New Drugs

**To:** Jane Liedtka, MD, Clinical Reviewer  
Jill Lindstrom, MD, Clinical Team Leader  
Division of Dental and Dermatology Products (DDDP)

**Re:** pediatric labeling

**Sponsor:** Topaz Pharmaceuticals

**Drug:** Sklice® (ivermectin)

**NDA:** 202736

**Supporting Doc:** Original Application, April 7, 2011 (Seq # 0001)

**Indication (proposed):** treatment of head lice in patients 6 months and older

**Dosage form/ strength:** topical cream 0.5% (5 mg ivermectin/gm of cream)

**Proposed dosing:** one 10 minute application to scalp to coat hair and scalp  
(maximum 4 oz (b)(4))

**Consult Question:**

DDDP requested PMHS input on the proposed pediatric labeling for the Pediatric Use Section (8.4), and recommendations on language to reflect the safety concern of ivermectin neurotoxicity in young patients.

**Materials Reviewed:**

- Sponsor Labeling from original NDA submission, April 7, 2011
- Labeling for Natroba™ (spinosad) Suspension, NDA 22-408 (January 18, 2011)

**Background:**

DDDP intends to approve NDA 202736 for Sklice® (ivermectin) for the treatment of head lice in patients 6 months and older. PREA required studies will be considered fulfilled in patients 6 months and older and waived in patients less than 6 months. A partial waiver will be granted in the youngest infants secondary to information strongly suggesting the product would be unsafe, i.e. young infants may be at higher risk of ivermectin neurotoxicity secondary to increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier. Please see the PMHS Consult August 2011 for additional details.

**Sponsor's Proposed Labeling:**



*If a waiver or partial waiver is granted due to a safety concern, the concern must be included in labeling. The Sponsor's proposal does not address the concern that young infants may be at higher risk of ivermectin neurotoxicity. The following additional language is recommended for inclusion in the Pediatric Use section (8.4):*

“The safety and effectiveness of SKLICE Topical Cream have not been established in pediatric patients below the age of 6 months. Young infants may be at higher risk of ivermectin neurotoxicity secondary to increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.”

*Additional labeling suggestions are provided below to be more consistent with 21 CFR 201.57:*

Highlights:

~~-----USE IN SPECIFIC POPULATIONS-----~~

***Pediatric Use: Safety and effectiveness in pediatric patients below the age of 6 months have not been established. (8.4)***

Pediatric Use (8.4):

*The safety and effectiveness of SKLICE Topical Cream have been established in **pediatric patients 6 months of age and older** {see Pharmacokinetics (12.3) and Clinical Studies (14)}.*

***The safety and effectiveness of SKLICE Topical Cream have not been established in pediatric patients below the age of 6 months. Young infants may be at higher risk of ivermectin neurotoxicity secondary to increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.***

PMHS participated in pediatric labeling discussions with the Division on October 25, 2011.

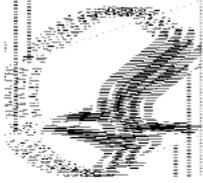
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/s/  
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ELIZABETH L DURMOWICZ  
11/08/2011

HARI C SACHS  
11/08/2011  
I concur!

LISA L MATHIS  
11/09/2011



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      **Public Health Service**

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Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
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**Addendum to Pediatric and Maternal Health Staff Review**

**Date:** October 24, 2011                      **Date Consulted:** May 20, 2011

**From:** Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst  
Pediatric and Maternal Health Staff

**Through:** Lisa Mathis, M.D., OND Associate Director,  
Pediatric and Maternal Health Staff

**To:** Division of Dermatology and Dental Products (DDDP)

**Drug:** SKLICE (ivermectin) Topical Cream, 0.5%, NDA 202-736

**Subject:** Pregnancy and Nursing Mothers Labeling

**Materials Reviewed:**

- Sponsor Labeling, submitted April 7, 2011

## **INTRODUCTION**

On April 7, 2011, Topaz Pharmaceuticals submitted a 505(b)(2) New Drug Application (NDA 202-736), for SKLICE (ivermectin) Topical Cream, 0.5%, for the treatment of head lice (b) (4) in patients 6 months of age and older. Topaz Pharmaceuticals references the nonclinical toxicology data and the clinical safety data from Merck's oral ivermectin product, Stromectol Tablets, NDA 50-742, in support of their application.

The Division of Dermatology and Dental Products (DDDP) consulted the Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team (MHT) on May 20, 2011, to review and recommend the appropriate pregnancy category for SKLICE (ivermectin) Topical Cream, 0.5%. PMHS-MHT provided a consult review to DDDP dated July 19, 2011 and recommended that the product be labeled as a pregnancy category C based on available data and current regulatory requirements. Subsequent to the PMHS-MHT review, DDDP requested PMHS-MHT input on pregnancy and nursing mothers labeling for SKLICE (ivermectin) Topical Cream, 0.5%.

## **SUBMITTED SPONSOR LABELING**



## **PMHS-MHT LABELING RECOMMENDATIONS**

The following is the SKLICE pregnancy and nursing mothers language agreed upon during an October 4, 2011 labeling meeting with DDDP.

### **8.1 Pregnancy**

#### Pregnancy Category C

There are no adequate and well-controlled studies with SKLICE Topical Cream in pregnant women. SKLICE Topical Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No comparisons of animal exposure with human exposure are provided in this label due to the low systemic exposure noted in the clinical pharmacokinetic study [*see Clinical Pharmacology (12.3)*].

#### Human Data

There are published reports of ivermectin use during human pregnancy. In an open label study, 397 women in their second trimester of pregnancy were treated with ivermectin and albendazole at the labeled dose rate for soil-transmitted helminths and compared with a pregnant, non-treated population. No differences in pregnancy outcomes were observed between treated and untreated populations.

#### Animal Data

Systemic embryofetal development studies were conducted in mice, rats and rabbits. Oral doses of 0.1, 0.2, 0.4, 0.8, and 1.6 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–15) to pregnant female mice. Maternal death occurred at 0.4 mg/kg/day and above. Cleft palate occurred in the fetuses from the 0.4, 0.8, and 1.6 mg/kg/day groups. Exencephaly was seen in the fetuses from the 0.8 mg/kg group. Oral doses of 2.5, 5, and 10 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–17) to pregnant female rats. Maternal death and pre-implantation loss occurred at 10 mg/kg/day. Cleft palate and wavy ribs were seen in fetuses from the 10 mg/kg/day group. Oral doses of 1.5, 3, and 6 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. Maternal toxicity and abortion occurred at 6 mg/kg/day. Cleft palate and clubbed forepaws occurred in the fetuses from the 3 and 6 mg/kg groups. These teratogenic effects were found only at or near doses that were maternally toxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus.

### **8.3 Nursing Mothers**

Following oral administration, ivermectin is excreted in human milk in low concentrations. This has not been evaluated following topical administration. Caution should be exercised when SKLICE Topical Cream is administered to a nursing woman.

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JEANINE A BEST  
10/24/2011

LISA L MATHIS  
10/25/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: October 14, 2011

Reviewer(s): Manizheh Siahpoushan, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, Pharm.D.  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Sklice (Ivermectin) Topical Lotion  
0.5%

Application Type/Number: NDA 202736

Applicant/sponsor: Topaz Pharmaceuticals

OSE RCM #: 2011-3184

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review evaluates the container closure system, container label, carton labeling, Prescribing Information, and Patient Instructions for Use for Sklice (Ivermectin) Topical Lotion, 0.5% (NDA 202736), submitted on October 11, 2011, for any areas of concern from a medication errors perspective.

### **1.1 PRODUCT INFORMATION**

Sklice (Ivermectin) Lotion 0.5% is an antiparasitic indicated for the topical treatment of head lice (b) (4) in patients 6 months of age and older. Sklice is applied to dry hair in an amount sufficient (up to 1 tube) to thoroughly coat the hair and scalp, and rinsed off with water after 10 minutes. This product is indicated for a one time use. This product will not have directions for a repeat dose as it is not necessary. This is different from all other lice treatment products which contain instructions for repeat dosing.

Sklice is supplied in a four ounce non child-resistant, blind-end laminate tube with peel seal container closure, and can be stored at room temperature.

## **2 METHODS AND MATERIALS**

### **2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA**

Because oral Ivermectin (established name for Stromectol) tablets, 3 mg, NDA 050742, has been marketed since November 22, 1996, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors related to labels and labeling, involving Ivermectin.

The September 12, 2011 AERS search used the following search terms: active ingredient “Ivermectin” and verbatim term “Ivermec%”. The reaction terms used were the MedDRA High Level Group Term (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error (e.g. adverse drug reactions unrelated to a medication error, allergic reactions, and suicide attempts).

## **2.2 LABELS AND LABELING RISK ASSESSMENT**

Using Failure Mode and Effects Analysis<sup>1</sup>, the principals of human factors, and the lessons learned from postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following (see Appendices A-B):

- Container closure system
- Container labels submitted 10/11/11
- Carton labeling submitted 10/11/11
- Prescribing Information submitted 10/11/11
- Patient Instructions for Use submitted 10/11/11

## **3 RESULTS**

The following sections describe the results of the DMEPA's medication error searches and labels and labeling risk assessment.

### **3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH RESULTS**

DMEPA retrieved 74 reports. After eliminating reports as described in Section 2, no cases relating to the label and labeling of Ivermectin remained.

### **3.2 LABELS AND LABELING RISK ASSESSMENT**

Our evaluation of the proposed container closure system, container label, carton labeling, Prescribing Information, and Patient Instructions for Use, identified the following deficiencies:

- The container closure of a laminated tube does not include a child resistant safety cap.
- The graphic design next to the proprietary name on the container labels and carton labeling can distract attention from the proprietary name, the established name, and the product strength.
- The 'Rx Only' statement on the principal display panel (both the container label and the carton labeling) and the back panel (carton labeling) is prominent and distracts from other important information such as the route of administration statement.
- The route of administration statement lacks prominence on the principal display panel (both the container label and the carton labeling) and the back panel (carton labeling), and is not displayed on the side panels of the carton labeling.
- The multi-color graphic design on the principal display panel (both the container label and the carton labeling) and the back panel (carton labeling) is prominent

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

and detracts from important information such as the name, strength, route of administration, and the warning statement (For single use. Discard the tube after use).

- The warning statement ‘For single use. Discard the tube after use.’ Lacks prominence and is not included on the principal display panel of the carton labeling.
- The warning statement [REDACTED] (b) (4) in the Dosage and Administration Section of both the Highlights and the Full Prescribing Information includes the incorrect route of administration.

#### 4 DISCUSSION

The container closure system of this proposed topical product is not child-resistant. Although, most topical products in the same type of container closure (laminated tube) have been used in the past for topical products, there is a concern that this product may cause serious adverse events if there were accidental pediatric exposures. Additionally, a laminated tube resembling container closure systems used for toothpastes, hand, or body lotions, is not the best option for the lice treatment indication. Errors in wrong route of administration have been reported to the Agency when the container closure is incongruent with the dosage and administration of the product. In this case, although the product is applied topically, it is only applied to the scalp. Thus, container closure system similar to a shampoo bottle that contains a child-resistant closure system may be a more appropriate option for lice treatment indication. Otherwise, we may encounter use of the product on other areas of the body.

At the Mid-Cycle meeting on September 19, 2011, the medical officer stated a concern that each tube of this product contains the equivalent of [REDACTED] (b) (4) Ivermectin tablets or [REDACTED] (b) (4) of Ivermectin. This is approximately [REDACTED] (b) (4) more drug than what is supplied in the unit dose package of Stromectol (supplied as unit dose packages of 20). Accidental pediatric exposure to this product may occur because the container closure does not contain a child-resistant cap. We have experienced similar accidental exposures with Lindane. The Division states that ingestion of even a partial tube could result in serious adverse events.

Additionally, although this product is intended as a single use product, the current practice of medicine used to treat lice can include repeat dosing of currently approved lice treatments. Thus, the Division is concerned that parents and caregivers may save a partial tube to repeat the dose in patients. Storing a partial tube of this product without child-resistant packaging could also lead to accidental exposures. Warning statements can be included in the labels and labeling, however, the best option for minimizing accidental exposures would include physical safe guards such as child-resistant packaging. Additionally, we note that the proposed quantity of 4 oz [REDACTED] (b) (4) is more than the usual quantity of 60 gram (or 60 mL) normally seen with lice treatment products. The large quantity of 4 oz may provide more opportunity for unused portions of the product to remain, and therefore a higher risk for accidental pediatric exposures. We defer to the Division to determine if the proposed quantity of 4 oz is appropriate for this

product. However, if possible, limiting the quantity in the bottle may decrease the risk if accidental ingestion were to occur.

The Division and DMEPA discussed our concerns with the Applicant via teleconference on September 20, 2011. The Applicant responded by submitting revised labels and labeling on October 11, 2011. The Applicant included the warning statement ‘For single use. Discard the tube after use’ in the Dosage and Administration Section of both the Highlights and the Full Prescribing Information, Patient Instructions for Use, as well as the container labels and carton labeling. However, the Applicant did not propose a physical barrier such as a child-resistant packaging configuration for this product. Although the addition of warning statements to alert patients and healthcare professionals that the product is for single use may reduce the risk of accidental pediatric exposure, it is still possible that patients may not discard the unused portion after use, which could increase the risk of accidental pediatric oral ingestion.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

Our evaluation of the proposed container closure system, container label, carton labeling, Prescribing Information, and Patient Instructions for Use, identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations for Prescribing Information and container closure in Section 5.1 *Comments to the Division*. We provide recommendations for the container labels and carton labeling in Section 5.2 *Comments to the Applicant*. We request these recommendations be implemented prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Janet Anderson 301-796-0675.

### **5.1 COMMENTS TO THE DIVISION**

1. The container closure should be re-designed to decrease the risk of accidental ingestions. Additionally, the container closure should resemble a shampoo or scalp product rather than a topical hand cream or lotion. If the container closure can not be redesigned then at a minimum the closure should be child-resistant.
2. The proposed quantity of 4 oz (b)(4) is more than the usual quantity of 60 gram (or 60 mL) normally seen with lice treatment products. The large quantity of 4 oz may provide more opportunity for unused portions of the product to remain, and therefore a higher risk for accidental pediatric exposures. If possible, limit the amount of product. We defer to the Division to determine if the proposed quantity of 4 oz is appropriate for this product.
3. The Dosage and Administration Section of the Highlights and the Full Prescribing Information contains the wrong route of administration statement (b)(4). The statement should be revised to state ‘For topical use on the scalp hair and scalp only. Sklice Topical Lotion should not be administered by any other routes of administration.’

## 5.2 COMMENTS TO THE APPLICANT

### A. Container Label and Carton Labeling

1. Delete the graphic presentation next to the proprietary name. As currently presented, the graphic can distract from the proprietary name, the established name, and the product strength.
2. Increase the font size of the dosage form and the strength statements (Topical Lotion 0.5%) that appear under the established name on the principal display panels, side panels, or the back panels of the container label and the carton labeling, to appear the same size as the established name. Additionally, relocate the strength statement, 0.5% to immediately under the dosage form. Increasing the font size of the dosage form and the strength statements will provide more prominence to these statements.
3. Delete the multi-color graphic on the container label and the carton labeling. The multi-color graphic, especially the purple portion of the graphic design can distract from other important information such as the product name, the route of administration, and the warning statements.
4. Relocate the 'Rx Only' statement to the bottom portion of the principal display panel of both the container label and the carton labeling. Additionally, unbold the 'Rx Only' statement. As currently presented, 'Rx Only' is placed in close proximity to the route of administration statement and distracts from the important warning statement, 'For Topical use on the scalp hair and scalp only'.
5. Increase the prominence of the route of administration statement by bolding the statement. Additionally, move the route of administration statement up, and closer to the dosage form and strength statements. As currently presented, the statement 'For topical use on the scalp hair and scalp only' lacks prominence.
6. Relocate (b) (4) (b) (4) from the top portion of the principal display panel of both the container label and the carton labeling to the bottom portion of the principal display panel, and decrease the font size of (b) (4). As currently presented, the name (b) (4) is too prominent and too close to the proprietary name, and may be misinterpreted as the proprietary name.
7. Relocate the warning statements 'Keep out of reach of children. Use in children should be under the direct supervision of an adult. Avoid eye contact.' To the principal display panel of the carton labeling and the front of the container label. Relocating the important warning statements provides more prominence to the statements.

## B. Container Label

1. Include the route of administration on the back panel of the container label. As currently presented, the statement 'For topical use on the scalp hair and scalp only' does not appear on the back panel. This statement may appear under the product dosage form and strength (Topical Lotion 0.5%).
2. Relocate the warning statement 'For single use. Discard the tube after use.' Further up on the principal display panel, and closer to the other warning statement 'for topical use on the scalp hair and scalp only'. As currently presented, the warning statement 'For single use. Discard the tube after use.' lacks prominence.

## C. Carton Labeling

1. Include the warning statement 'For single use. Discard the tube after use.' On the principal display panel of the carton labeling. As currently presented, this statement appears only on the top and bottom closure flaps and lacks prominence.
2. Relocate the 'Rx Only' statement to the bottom portion of the back panel of the carton labeling. Additionally, unbold the 'Rx Only' statement. As currently presented, 'Rx Only' is placed in close proximity to the route of administration statement and distracts from the important warning statement, 'For Topical use on the scalp hair and scalp only'.
3. Delete the (b) (4) (b) (4) on the back panel of the carton labeling. As currently presented, the name (b) (4) is too prominent and distracts from the product quantity statement. Additionally, the company name appears on the principal display panel.
4. Increase the prominence of the route of administration statement on the back panel of the carton labeling by bolding the statement. As currently presented, the statement 'For topical use on the scalp hair and scalp only' lacks prominence.
5. Include the route of administration statement on the side panels of the carton labeling. As currently presented, the statement 'For topical use on the scalp hair and scalp only' does not appear on the side panels. The statement may appear under the product dosage form and strength (Topical Lotion 0.5%).

## **6 REFERENCES**

### **1. ADVERSE EVENTS REPORTING SYSTEM (AERS)**

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

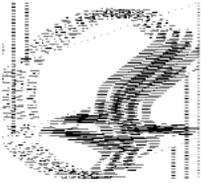
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MANIZHEH SIAHPOUSHAN  
10/14/2011

ZACHARY A OLESZCZUK  
10/14/2011

CAROL A HOLQUIST  
10/14/2011



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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**M E M O R A N D U M**

**Date:** August 24, 2011

**From:** Elizabeth L. Durmowicz, MD, Medical Officer

**Through:** Hari Cheryl Sachs, MD, Team Leader  
Lisa Mathis, MD, OND Associate Director  
Pediatric and Maternal Health Staff, Office of New Drugs

**To:** Jane Liedtka, MD, Clinical Reviewer  
Jill Lindstrom, MD, Clinical Team Leader  
Division of Dental and Dermatology Products (DDDP)

**Re:** adequacy of the pediatric safety database in patients less than 2 years

**Sponsor:** Topaz Pharmaceuticals

**Drug:** Sklice® (ivermectin)

**NDA:** 202736

**Supporting Doc:** Original Application, April 7, 2011 (Seq # 0001)

**Indication (proposed):** treatment of head lice in patients 6 months and older

**Dosage form/ strength:** topical cream 0.5% (5 mg ivermectin/gm of cream)

**Proposed dosing:** one 10 minute application to scalp to coat hair and scalp  
(maximum 4 oz (b) (4))

**Consult Question:**  
“Is the safety database provided in NDA 202736 sufficient with regard to age group 6 months to 2 years to allow approval in this age group?”

**Materials Reviewed:**

- Sponsor's request for a partial waiver of pediatric studies (February 28, 2011)
- Special Protocol Agreement, IND 73,134 (December 23, 2009)
- PMHS Consult for Natroba™ (spinosad) Suspension, NDA 22-408 (October 6, 2010)
- PMHS Consult for malathion gel, NDA (b)(4) (February 7, 2011)
- Approval letters for Ulesfia™, NDA 22-129, (April 9, 2009) and Natroba™, NDA 22-408 (January 18, 2011)
- Division of Drug Risk Evaluation Review of Stromectol® (March 31, 2005)
- Meeting Minutes, End of Phase 2 meeting IND 73,134 on August 12, 2009 (August 26, 2009)
- Memorandum to IND 73,134, Pharmacology/Toxicology Review (January 8, 2008)
- DDDP Memorandum Helioblock SX Cream NDA 22-009 (February 10, 2008)

**Regulatory Background:**

NDA 202736 for Sklice® (ivermectin) for the treatment of head lice in patients 6 months and older was submitted April 7, 2011 as a 505(b)(2) application. The principal presubmission activities included a Pre-IND meeting (July 2006), a Guidance Meeting (November 2008) and an End of Phase 2 (EOP2) meeting (August 2009). In addition, the design of the two pivotal studies was the subject of a Special Protocol Assessment (SPA), for which an agreement was reached in December 2009.

PREA is triggered by the application due to a new indication, new dosage form and new dosing regimen for ivermectin. A partial waiver of studies under PREA was requested in patients birth to less than 6 months, secondary to too few patients to study and evidence strongly suggesting that the drug would be unsafe.

**Reviewer Comment:**

*See below for a discussion of the partial waiver request.*

**Ivermectin:**

Ivermectin is an anthelmintic derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents. Per the literature, ivermectin blocks transmission across glutamate and  $\gamma$ -aminobutyric acid (GABA) nerve synapses. Although GABA and glutamate do not act on the peripheral motor function of the body, GABA is a neurotransmitter in the spinal cord, cerebellum, basal ganglia, and areas of the brain cortex and glutamate is a neurotransmitter in many of the sensory pathways and in many areas of the brain cortex. Hence, if ivermectin crosses the blood-brain barrier<sup>4</sup>, serious toxicity, including depression, tremors, ataxia, coma and breathing difficulties, can occur<sup>3,4</sup>. Ivermectin has been used extensively as a topical, oral and injectable (subcutaneous) agent in veterinary medicine<sup>3</sup>.

Originally approved in 1996, Stromectol® (NDA 50-742), ivermectin oral tablets (3 and 6 mg), is indicated for the treatment of strongyloidiasis of the intestinal tract and

onchocerciasis in patients 15 kg or greater. Labeling states that the avermectins have a low affinity for mammalian ligand-gated chloride channels, and that ivermectin does not readily cross the blood-brain barrier in humans. Labeling warns of specific adverse reactions associated with use in patients with onchocerciasis, specifically cutaneous and systemic reactions (the Mazzotti reaction), ophthalmological reactions and encephalopathy. No other adverse events are included in Warnings or Precautions. Per Stromectol® labeling, elevation in ALT and/or AST was identified in 2% of patients in clinical trials (n=109 treated with one or two doses of ivermectin).

**Reviewer Comment:**

*When considering use of ivermectin in patients less than 15 kg, the unapproved age group for the approved ivermectin product, and potential off-label use of Sklice® in patients younger than 6 months, review of the potential for ivermectin to cross the blood-brain barrier and interfere with glutamate and GABA transmission is warranted. The literature raises the concern that younger patients may be at higher risk of ivermectin neurotoxicity secondary to the immaturity of the blood-brain barrier<sup>3,4</sup>, but definitive data, including a specific definition of “younger”, does not appear to be available.*

*The role and maturity of P-glycoprotein (P-gp) is an important consideration in the safety of ivermectin use in infants. P-gp is located in brain capillary endothelial cells and plays an important role in the blood-brain barrier by actively transporting a large variety of substances, including, drugs such as ivermectin<sup>12,16</sup>, out of the cell. Per the literature, knockout mice lacking detectable P-gp and a subpopulation of Collie dogs with a mutation that impairs P-gp function display approximately 100-fold increased sensitivity to ivermectin and highly increased brain penetration of ivermectin compared to normal mice and Beagle dogs, respectively<sup>15,16</sup>. Data regarding the developmental expression of P-gp in the human central nervous system appear to be limited<sup>7</sup>. Studies in the mouse and rat have indicated that the fetal brain expresses a relatively low level of P-gp, but expression dramatically increases by term<sup>10,12</sup>. Ek concluded that although 3 of 4 transporter genes studied in rats were already expressed in the fetus at levels comparable to the adult, P-gp expression increased with age, and that the developing brain barrier is a dynamic process<sup>10</sup>. Hence, in summary, data do not appear to be available to determine when the blood-brain barrier and P-gp are mature in young infants.*

**Head lice and pediatric patients:**

Per the literature, head lice infestation in pediatric patients is a common problem especially in patients 3-12 years, and their families. Although over-the-counter pediculicides have been available for 30 years and are still recommended by most treatment guidelines as initial therapies, genetic alterations in the louse has resulted in resistance to currently available therapies, and alternative therapies are now often necessary<sup>3</sup>.

**Sklice®:**

The proposed indication for Sklice®, ivermectin 0.5% topical cream, is the treatment of head lice in patients 6 months and older. Data to support the application include data from 7 clinical and 7 nonclinical trials conducted with topical ivermectin, and nonclinical

and safety data for oral ivermectin, i.e. Stromectol®, NDA 50-742 (see Appendix I for the list of the clinical studies).

**Dosing:**

The proposed dosing is to apply Sklice® Cream in an amount sufficient to coat the hair and scalp (maximum 1 tube/4 ounces (b)(4)). After 10 minutes, the cream is to be rinsed off with water.

*In vitro* testing was performed to assist in dose selection. Per the Draft Clinical Review (July 20, 2011), the Sponsor demonstrated that the killing effect of ivermectin cream plateaued at 0.5%, a 10 minute application time was optimal and lower concentrations of ivermectin, 0.15% and 0.25%, were not as efficacious. Clinical study TOP003 demonstrated that lower ivermectin cream concentrations did not demonstrate marked differences in efficacy, and no differences in safety.

**Reviewer Comment:**

*Although extrapolation of dosing is not generally permitted, given that ivermectin cream works on contact with head lice (b)(4) the effective killing dose is expected to be the same in all patients. However, the safety of the proposed dosing must be established in all pediatric subgroups (more below).*

**Efficacy:**

Efficacy data submitted to support approval include data from two pivotal Phase 3 studies, (TOP011 and TOP012), and supportive efficacy data from a phase 2b (TOP010) and phase 2 dose-ranging study (TOP003). Identical in design, the pivotal studies (TOP011 and TOP012) were double-blind, randomized trials comparing the efficacy, safety and local tolerability of 0.5% ivermectin cream (n=410) compared to topical vehicle control (n=371) in patients 6 months of age and older with *Pediculus humanus capitis* infestation. The primary efficacy endpoint in the pivotal studies was the proportion of patients who were lice free on Day 15.

**Reviewer Comment:**

*Analysis of the efficacy data is deferred to the clinical reviewer.*

**Safety:**

To support the safety of topical 0.5% topical cream the Sponsor submitted nonclinical data, clinical study data including evaluations of systemic absorption, adverse events, and laboratory analysis, and articles from the literature.

Nonclinical Data:

A repeat dose dermal toxicity study of ivermectin was performed and reviewed previously under IND 73,134. No treatment-related dermal or systemic toxicity was noted in the study, and the NOAEL was identified as 4% ivermectin shampoo/conditioner (13 mg/kg/day) after 14 days of dermal administration (1 hour/day). The systemic concentrations of ivermectin during the initial 24 hours of exposure were below limit of quantification (BLQ 5 ng/mL). Following 14 consecutive days of dosing, the maximum

concentration was 10.62 ng/mL. Of note, for comparison, per the Clinical Pharmacology reviewer, the apparent C<sub>max</sub> (mean ± SD) following oral administration of ivermectin to patients 4 to 10 years was 41.83 ± 20.44 ng/mL (more below).

In addition, two, 2-week oral systemic toxicity studies were conducted in juvenile animals. The NOAELs for oral ivermectin were the highest doses studied, i.e. 0.1 mg/kg/day for neonatal rhesus monkeys (7-13 days of age) and 1.2 mg/kg/day for immature rhesus monkeys (13-21 months of age). No toxicokinetic data are available. The systemic toxicology studies in juvenile animals did not identify a significantly different toxicity profile of ivermectin compared to the studies in adult animals (personal correspondence, Jianyong Wang, Ph.D., August 11, 2011).

The levels of the excipients are considered acceptable from a pharmacology/toxicology perspective.

**Reviewer Comment:**

*Per the nonclinical review (January 2008), the combination of the systemic nonclinical toxicology data available for Stromectol® tablets and the studies conducted by the sponsor with the topical ivermectin formulation are adequate to support the proposed application.*

**Systemic Absorption:**

To evaluate the extent of systemic absorption, two pharmacokinetic (PK) studies were performed, TOP001 and TOP008. Both studies also performed an assessment of adverse events (AEs) and laboratory monitoring, including liver function tests (LFTs) and complete blood counts (CBCs).

**Study TOP001:**

TOP001 was a randomized PK and safety study, with double blind and open-label components, of 0.5% ivermectin in a topical shampoo/conditioner preparation (n=15) compared to ivermectin orally (n=6) and topical placebo (n=5) in patients 4-10 years. Per the Sponsor, no evidence of systemic ivermectin absorption (limit of quantification, LLOQ: 5 ng/mL) was detected in the topical ivermectin treatment group (n=12 evaluable patients). The oral ivermectin treated patients (n=4 evaluable patients) had levels consistent with the known pharmacokinetics of Stromectol® per product labeling. The mean dose was 168.7 µg/kg (range: 133.3 to 228.1 µg/kg). Per the Clinical Pharmacology reviewer, the apparent C<sub>max</sub> (mean ± SD) following oral administration was 41.83 ± 20.44 ng/mL, n.b. calculation of AUC was not possible due to the limited amount of data (personal correspondence between Hari Sachs and Chinmay Shukla, 7/15/2011).

**Reviewer Comment:**

*Per personal correspondence with the clinical reviewer, Jane Liedtka MD (August 1, 2011), CMC determined that the shampoo/conditioner ivermectin formulation used in study TOP001 was comparable to the proposed to-be-marketed formulation, and*

*therefore, the data collected from the shampoo/conditioner formulation are able to be used to support the application.*

*Of note, study TOP001 used a less sensitive bioanalytical method than the method used in the other PK study, TOP008; the method used in TOP001 had a LLOQ of 5 ng/mL and the method used in TOP008 had a LLOQ of 0.05 ng/mL (more below). The Sponsor reanalyzed the samples from TOP001 with the more sensitive method, but the reanalyzed data are not reliable secondary to an inadequacy of stability data to support the reanalysis (personal correspondence between Hari Sachs and the Clinical Pharmacology Reviewer, Chinmay Shukla, 7/15/2011). However, the original results are considered reliable and appear to indicate that systemic absorption is minimal and per Dr. Shulka, the C<sub>max</sub> following topical administration is at least 8-fold lower than the C<sub>max</sub> following oral administration in patients 4-10 years.*

*No safety signals were identified based on study adverse events and laboratory monitoring (more below).*

**Study TOP008:**

TOP008 was an open-label Phase 1 PK, safety and efficacy study of a single 10 minute application of 0.5% ivermectin cream to 30 pediatric patients 6 months to 3 years of age. Per the Sponsor, 24 patients weighed less than 15 kg and 12 of these patients were aged 6 months to 2 years. The treatment amount, i.e. amount of cream applied, was 6.3-98.8 gm (mean dose  $\pm$  SD: 19.1  $\pm$  9.4 mg/kg). The first 20 patients had PK analysis performed using a plasma ivermectin test with a LLOQ of 0.05 ng/mL. In one patient, ivermectin was not detected in any samples, and in the remaining 19 patients, the C<sub>max</sub> (mean  $\pm$  SD) was 0.241  $\pm$  0.234 ng/mL (range 0.06 at 24 hours post application to 0.97 ng/mL at approximately one hour post rinsing). Per the nonclinical reviewer, AUC<sub>last</sub> (mean  $\pm$  SD) was 6.701  $\pm$  11.23 ng h/mL, and AUC<sub>0-24</sub> (mean  $\pm$  SD) was 3.972  $\pm$  3.514 ng h/mL following topical administration. Per Dr. Shulka, cross study comparison of the PK data from study TOP008 and TOP001 identifies that the mean C<sub>max</sub> following topical administration (0.241  $\pm$  0.234 ng/mL) is approximately 200 fold lower in the patients 6 months to three years than the mean C<sub>max</sub> following oral administration (41.83  $\pm$  20.44 ng/mL) in patients 4 to 10 years. Per the Sponsor, no safety signals were identified from the analysis of CBCs and LFTs and all adverse events were mild or moderate in intensity.

Of note, during the EOP2 meeting in August 2009, the Agency recommend that the Sponsor enroll a minimum of 15 subjects with a minimum of 12 evaluable subjects completing the study with at least half of the subjects below the age of 2 years.

**Reviewer Comment:**

*Given that the PK data appear to support that limited ivermectin is absorbed after topical application and that the dermis is considered mature at age 6 months, the available PK data appear to be adequate to determine that only minimal systemic absorption occurs in patients 6 months of age and older. However, the adequacy of the PK data in patients less than 12 months of age is deferred to the Clinical Pharmacology reviewer.*

*Per review of the ages of the patients for which PK data were obtained, the Sponsor evaluated PK in 7 patients less than 2 years, a number of patients consistent with the recommendations made by the Agency in the EOP2 meeting. Two patients were 18-24 months, 4 patients were 12-23 months and 1 patient was less than 12 months of age, i.e. age 6 months. Although the patients 12-23 months received doses of Sklice® cream close to or greater than the mean dose of 19.1 gm, i.e. 18.3 gm, 24.7 gm, 32.5 gm, 33.5 gm, 39.4 gm, 87.8 gm, the 6 month old patient received the lowest dose administered in the study, i.e. 6.3 grams of cream. This patient weighed 18.8 lbs (8.5 kg), a weight between the 85<sup>th</sup> and 97<sup>th</sup> percentile for age based on the WHO growth charts<sup>19</sup>. The difference in the relative surface area of the head is small in infants less than 1 year compared to children ages 1 year to 5 years (half of the head in infants less than 1 year is 9½% of the total body surface area (BSA) versus half of the head in patients 1 to less than 5 years is 8½% of the BSA), and may not substantially affect the amount of ivermectin cream absorbed.<sup>14</sup> Nonetheless, given that PK data are available only for one patient less than 12 months, a relatively large child that was administered a low dose (below the mean dose minus the standard deviation), the Clinical Pharmacology should be satisfied that the data are adequate to support minimal absorption in the less than 12 month age group.*

*No safety signals were identified based on study adverse events and laboratory monitoring (more below).*

**Safety Data from the Sponsor’s Clinical Trials:**

Per the Sponsor, the integrated analysis of safety includes all patients treated with 0.05% ivermectin cream from the seven clinical studies performed (n=901). Table 1 provides the ages of the patients included in the safety analysis and is an excerpt from the Sponsor’s Summary of Clinical Safety Table 16 “Demographic Characteristics: Safety Population: All Studies”:

**Table 1:** Age of Patients in the Safety Analysis

Age (years): n (%)	Missing	1 (0.1%)	1 (0.1%)
	0.5 to < 2	21 (2.3%)	8 (1.1%)
	2 to < 4	67 (7.4%)	40 (5.3%)
	4 to < 12	291 (32.3%)	241 (32.1%)
	12 to 16	103 (11.4%)	66 (8.8%)
	> 16	418 (46.4%)	394 (52.5%)

Per the Sponsor, the incidence, severity, and relationship to study medication of adverse events (AEs) were similar between treatment groups across all of the studies. A total of 196 AEs were reported, approximately 80% of the AEs in each treatment group were mild in severity, and more than 95% of the AEs in treatment group were either mild or moderate. Only 6 AEs (3 in each treatment group) were severe. The majority of AEs in each treatment group (0.5% ivermectin group: 65%; vehicle control group: 58%) were considered unrelated to study medication. Across all of the Sponsor studies, 1 patient, an 8 month old infant from study TOP008, experienced serious adverse events (SAEs). This

patient was hospitalized due to 3 SAEs, i.e., acute gastroenteritis, dehydration, and diaper dermatitis. None of the SAEs was considered treatment-related by the Investigator.

AEs for the 6 month to less than 2 year age group were analyzed separately. Per the Sponsor, although percentages of AEs, subjects experiencing AEs, severity of AEs, and relationship of AEs to study medications were generally similar between treatment groups and among age groups, the 6 month to less than 2 year age cohort had a higher percentage of AEs and subjects experiencing AEs than the other age groups. However, per the Sponsor, the 2 treatment groups within the age group were similar to each other, i.e. 0.5% ivermectin group: 29%; vehicle control group: 25%, and the majority of AEs, i.e. 67% for both treatment groups, in this age group were mild and none was severe. As noted above, the patient in the clinical study program that experienced SAEs was in this age cohort, but the SAEs were not considered treatment related. More than 88% of the AEs occurring in this age group were considered unrelated to study medication, i.e. 89% 0.5% ivermectin group: 89% ; vehicle control group: 100%, and none were considered probably or definitely related.

**Reviewer Comment:**

*The detailed and comprehensive review of the safety data are deferred to the Clinical Reviewer; however, the adverse events and laboratory abnormalities identified in studies TOP001 and TOP 008 do not appear to identify a safety concern associated with the topical use of 0.5% ivermectin cream in pediatric patients, a finding that would be consistent with minimal systemic absorption.*

Literature to Support the Safety of Ivermectin:

To support the safety of topical 0.5% ivermectin cream for the treatment of head lice, the Sponsor also submitted publications from the literature and cited additional publications in the Summary of Clinical Safety. Per the Clinical Reviewer, the literature provides reassuring details on a large number of patients treated with oral ivermectin.

**Reviewer Comment:**

*Data from the literature support that oral ivermectin has been used extensively in patients 5 years of age and older for the treatment of onchocerciasis and lymphatic filariasis<sup>1,2,6,20</sup>. Per data published by Colatrella in 2008, more than 530 million oral ivermectin treatments for onchocerciasis have been administered since 1987, n.b. routine dose 150-200 µg/kg, or 3 -15 mg per dose for patients 15-79 kg<sup>6</sup>. In addition, the literature supports that both topical and oral ivermectin have been used in pediatric patients as young as 6 months for the treatment of head lice and scabies. However, limited information appears to be available on oral or topical ivermectin use in patients less than 2 years and/or less than 15 kg (see Appendix II for a summary of identified publications).*

Additional Safety Data:

In March 2005, the Division of Drug Risk Evaluation reviewed all AERS reports in pediatric patients 0-16 years, and AERS reports of seizures and hepatotoxicity in all patients treated with ivermectin. The pediatric review identified 33 unduplicated reports,

all reported as “serious”. Nine reports of death were identified, and ivermectin causality could not be ruled out in two cases, a case of fatal hepatitis in a 6 year old patient and a case of Stevens-Johnson Syndrome in a 14 year old. The other reports were either labeled or likely related to the disease process. The review of seizures and hepatotoxicity concluded that an association between ivermectin treatment and the occurrence of seizures and hepatotoxicity may exist. (DDRE Review, Evelyn Farinas, March 21, 2005).

**Question from the Division:**

**The safety database for the submission includes 30 pediatric patients between the ages of 6 months and 3 years (Study TOP008) and an additional 9 subjects treated with the investigational product in efficacy studies under the age of 2 years (combined TOP003, TOP010, TOP011 and TOP012). Is the safety database provided in NDA 202736 sufficient with regard to age group 6 months to 2 years to allow approval in this age group?**

***Reviewer Comment on the Division’s Question:***

*Presuming that the clinical data do not identify safety signals in pediatric patients, especially in patients 6 months to 2 years, and that the clinical pharmacology reviewer is satisfied that the data are adequate to support that systemic absorption in patients less than 2 years is minimal, the size of the safety database is acceptable to support approval in patients 6 months to two years. Although the data from the literature are limited in patients less than 2 years and less than 15 kg, the experience with oral ivermectin in the treatment of strongyloidiasis and onchocerciasis, and data from the literature of studies evaluating topical and oral ivermectin use in the treatment of pediatric patients as young as 6 months for scabies and head lice is reassuring.*

**Additional Comment on the PREA Requirement:**

The Sponsor has requested a partial waiver of studies under PREA in patients birth to less than 6 months, secondary to too few patients to study and evidence strongly suggesting that the drug would be unsafe. Proposed labeling does not reference the safety concern. The Sponsor states that patients less than 6 months of age were not included in the trial as safety in this age group has not been established, and note that potential exists for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.

***Reviewer Comment:***

*A partial waiver of studies under PREA may be granted if studies are*

- (i) impossible or highly impracticable,*
- (ii) evidence strongly suggests that the drug or biological product would be ineffective or unsafe in all pediatric age groups, or*
- (iii) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is not likely to be used in a substantial number of pediatric patients, n.b. both criteria must be met.*

*In addition, a partial waiver of studies in a pediatric subpopulation may be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation*

*necessary for that age group have failed. The attempts must be documented. Of note, if a waiver is granted due to a lack of efficacy or a safety concern, labeling must reflect the concern.*

*Two products were recently approved for the topical treatment of head lice infestation in pediatric patients, i.e. Ulesfia™ (5% benzyl alcohol) lotion, NDA 22-129 (April 2009) and Natroba™ (spinosad) topical suspension, NDA 22-408 (January 2011). Both were granted a partial waiver for pediatric studies less than 6 months of age, although the rationales differed.*

*Ulesfia™ was approved in patients 6 months and older. PREA studies were waived in patients 0-1 month due to too few patients to study, and in patients 1 to 6 months because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of patients. The approval letter notes that head lice infestation is not prevalent in children younger than six months of age and the standard treatment for children that age is to shave the head.*

*Although the active ingredient in Natroba™ is spinosad, the formulation contains 10% benzyl alcohol. PREA studies were waived in patients birth to 6 months for three reasons: the risk of benzyl alcohol toxicity, studies are impossible or highly impracticable because there are too few children to study, and the product does not represent a meaningful health benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients in this subpopulation. Labeling reflects the safety concern that resulted in the waiver of pediatric studies in this age group. The PREA requirement was deferred in patients 6 months to less than 4 years because the product was ready for approval in adults,*

*Discussion of Partial Waiver Criteria for Sklice®:*

*PMHS agrees that a partial waiver less than 6 months of age for topical ivermectin is appropriate. The Sponsor has proposed a partial waiver based on (1) too few patients to study, and (2) evidence strongly suggesting that the drug would be unsafe.*

*A partial waiver in this age group meets multiple criteria. Since studies in pediatric patients less than 6 months are not likely to be feasible because there are too few patients with head lice infestation in this patient population to study, a partial waiver based on this criterion (the first criterion) may be reasonable. In addition, given that the standard of care for patients less than 6 months of age does not include pharmacologic therapy, a waiver based on the third criteria, “the product does not represent a meaningful therapeutic benefit over existing therapies **and** is not likely to be used in a substantial number of patients”, is also appropriate.*

*In addition, PMHS believes a partial waiver based on evidence strongly suggesting that the drug would be unsafe (the second criterion) should be considered in the youngest infants, e.g. patients birth to less than 3 months, secondary to the risk of potential neurotoxicity. Although definitive data are lacking, the blood-brain barrier may be*

*immature in young infants. In addition, increased systemic absorption may occur due to the immature dermis and the relatively larger head to total body surface area. If a partial waiver is granted secondary to safety, the information regarding potential neurotoxicity must be included in labeling. Presuming off-label use [REDACTED] (b) (4) may be anticipated, discouraging use in young infants may be prudent.*

**Conclusions and Recommendations:**

Presuming that the clinical data do not identify safety signals in pediatric patients, especially in patients 6 months to 2 years, and that the clinical pharmacology reviewer is satisfied that the data are adequate to conclude that systemic absorption in patients less than 2 years is minimal, the safety database is acceptable to support approval in patients 6 months to two years.

A partial waiver of PREA required studies in patients birth to less than 6 months is reasonable. PMHS believes that a partial waiver based on safety should be granted because evidence strongly suggests that the product would be unsafe in the youngest infants, e.g. birth to 3 months. If a partial waiver is granted based on safety, the safety concerns regarding the potential for neurotoxicity must be included in labeling. For older infants, e.g. 3 months to less than 6 months, either a partial waiver based on “too few patients to study” or “the product does not represent a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients” would be appropriate. Of note, all PREA partial waivers must be reviewed by the Pediatric Review Committee (PeRC) before an action is taken.

**APPENDIX I: Tabular Listing of All Clinical Studies (from the Sponsor)**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/BA	TOP001	5.3.3.2.1	Compare PK of Ivermectin Cream to oral ivermectin; compare safety and tolerability of Ivermectin Cream to placebo	Randomized, with double-blind and open-label components Placebo and active controls	Topical Ivermectin 0.05% and placebo: 60 mL on scalp and into dry hair. A second dose was applied 9 to 11 days later if eradication was achieved on first dose Oral ivermectin: 150 µg/kg body weight with 6 oz water	26	Children with head lice infestation	10 minutes followed by rinse Single dose	Complete. Final.
BA	TOP008	5.3.3.2.2	Determine the BA of 0.5% Ivermectin Cream in a pediatric population	Open-label, multi-center, single application trial. No control.	0.5% Topical Ivermectin Cream	30	Pediatric patients 6 months to 3 years of age who had head lice infestation	One application for 10 minutes followed by rinse	Complete. Final.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	TOP011	5.3.5.1.1	Compare the efficacy of 0.5% Ivermectin Cream to vehicle control	Multi-site, randomized, double-blind, two-arm, parallel study Vehicle controlled	0.5% Topical Ivermectin Cream	410	Subjects with head lice infestation	Single dose, at-home application	Complete. Final.
Efficacy	TOP012	5.3.5.1.2	Compare the efficacy of 0.5% Ivermectin Cream to vehicle control	Multi-site, randomized, double-blind, two-arm, parallel study Vehicle controlled	0.5% Topical Ivermectin Cream	371	Subjects with head lice infestation	Single dose, at-home application	Complete. Final.
Safety	TOP010	5.3.5.1.3	Compare the safety and local tolerability of 0.5% Ivermectin Cream to vehicle control	Multi-center, randomized, double-blind, 2-arm, parallel study Vehicle control	0.5% Topical Ivermectin Cream	264	Subjects with head lice infestation	One application for 10 minutes followed by rinse	Complete. Final.

**APPENDIX II:** Published Literature on Ivermectin Use in Patients less than 2 years

<b>Author</b>	<b>Condition</b>	<b>Trial design</b>	<b>Formulation/ Dosing regimen</b>	<b>Age range/ number of patients received ivermectin</b>	<b>Findings:</b>
<b>Brooks</b> <sup>2</sup> 2002	Scabies	RCT	Oral, 200 µg/kg x1	6 months-14 years/ n=43	Ivermectin equally as effective as benzyl benzoate. No serious side effects noted
<b>Chosidow</b> <sup>5</sup> 2010	Head lice	RCT	Oral, 400 µg/kg x 2 (days 1 and 8)	Min 2 years (median age 10 years, interquartile range 7-14 years) Min wt. 15 kg (mean: 40 +/- 22kg)/ n=398	Ivermectin superior efficacy compared with topical 0.5% malathion; AEs similar across age groups.
<b>del Mar Saez-de-Ocariz</b> <sup>8</sup> 2002	Scabies (n=11) or cutaneous larva migrans (n=7)	Case series	Oral 150-200 µg/kg (one treatment n=15, 2 treatments n=3)	14 months – 17 years/ n=18	SE uncommon, one patient mild headache and dizziness x 4 hrs.
<b>Denion</b> <sup>9</sup> 2004	External ophthalmo- myiasis	Case series	Ophthalmic ointment	1.5 months – 39 years/ n=9	Ivermectin may help kill larvae before extraction
<b>Halpert</b> <sup>11</sup> 1998	Head lice	RCT	0.8% shampoo x 10 mins > 5 years, 5 mins < 5 years	2-25 years (avg. 8 +/-0.4 years )/ n=104	Ivermectin better than benzene hexachloride. No SE.  <i>Minimal data available.</i>
<b>Lawrence</b> <sup>13</sup> 2005	Scabies	Case/Pop control	Oral 160-250 µg/kg; day 1, sometimes day 15	Less than 12 years but ≥15 kg; n=541  <i>(details of trial difficult to understand)</i>	Prevalence of scabies fell.
<b>Victoria</b> <sup>18</sup> 2001	Scabies	OL	topical solution of 1% ivermectin, 400 mcg/kg dose x minimum of 2 hours	1-10 years (8 patients 1-3 years)/ n=19	All patients cured. No SE reported

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/s/  
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ELIZABETH L DURMOWICZ  
08/29/2011

HARI C SACHS  
08/29/2011  
I agree with the recommendations within this consult.

LISA L MATHIS  
08/30/2011



## INTRODUCTION

On April 7, 2011, Topaz Pharmaceuticals submitted a 505(b)(2) New Drug Application (NDA 202-736), for SKLICE (ivermectin) Topical Cream, 0.5%, for the treatment of head lice (b) (4) in patients 6 months of age and older. Topaz Pharmaceuticals references the nonclinical toxicology data and the clinical safety data from Merck's oral ivermectin product, Stromectol Tablets, NDA 50-742, in support of their application.

The Division of Dermatology and Dental Products (DDDP) consulted the Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team (MHT) on May 20, 2011, to review and recommend the appropriate pregnancy category for SKLICE (ivermectin) Topical Cream, 0.5%. The Sponsor has proposed a pregnancy category (b) (4) for this product based on (b) (4)

## BACKGROUND

### Ivermectin

Ivermectin is an anthelmintic that is derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation of products of *Streptomyces avermitilis*. Avermectins cause the death of parasites primarily through binding selectively and with high affinity to glutamate-gated chloride channels which occur in invertebrate nerve and muscle cells.

Oral ivermectin (Stromectol Tablets, NDA 50-742), was approved November 22, 1996, for the treatment of strongyloidiasis of the intestine tract and for the treatment of onchocerciasis. Stromectol tablets were classified as a pregnancy category C based on teratogenic findings in animals and a lack of adequate and well-controlled studies in pregnant women

### “PRECAUTIONS

*Pregnancy, Teratogenic Effects*  
*Pregnancy Category C*

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m<sup>2</sup>/day basis). Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.”<sup>1</sup>

### Review of Ivermectin Human Pregnancy Exposure Published Literature

PMHS found the following information on pregnancy outcomes with ivermectin exposure in published literature.

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<sup>1</sup> See current Stromectol labeling, December 15, 2009

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Topaz Pharmaceuticals did not conduct any nonclinical reproductive and developmental toxicology studies or adequate and well-controlled studies in pregnant women with ivermectin topical cream (b) (4)

The Sponsor is requesting a pregnancy category (b) (4) classification for SKLICE (ivermectin) Topical Cream, 0.5% based on (b) (4)

### SUBMITTED SPONSOR LABELING



#### *Reviewer Comments:*

1. *The Sponsor did not submit animal reproductive and developmental studies with SKLICE.* (b) (4)



**DISCUSSION**

Specific requirements on the content and format of pregnancy labeling for human prescription drug and biological products can be found in 21 CFR 201.57(c)(9)(i). See Appendix A for a summary of the pregnancy category definitions from the pregnancy labeling regulations. The pregnancy subsection of labeling is required for all drugs that are absorbed systemically. Both oral and topical ivermectin are systemically absorbed, with topical ivermectin showing a systemic concentration of about 8-fold lower<sup>2</sup> than the systemic concentration of oral ivermectin. Therefore, under the current labeling regulations, a pregnancy category is required for topical ivermectin because it is systemically absorbed, albeit at a lower amount.

The Sponsor has proposed a pregnancy category (b) (4) classification for their topical ivermectin product based on

(b) (4)

However, based on current regulations, the following conditions need to be satisfied for a drug to receive a pregnancy category (b) (4) classification:

(b) (4)

The Sponsor has not satisfied either requirement to receive a pregnancy category (b) (4) classification for their topical ivermectin product. The Sponsor reports in their NDA submission that they

(b) (4)

<sup>2</sup> Per the DDDP Clinical Pharmacology Reviewer based on the review of the submitted data

## **Pregnancy Labeling**

The Pregnancy subsection of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS- Maternal Health labeling recommendations comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

## **CONCLUSIONS AND RECOMMENDATIONS**

SKLICE (ivermectin) Topical Cream, 0.5%, should be classified as a pregnancy category C at this time as the Sponsor did not submit adequate data to classify the drug as a pregnancy category (b) (4). The Sponsor could establish a SKLICE pregnancy exposure registry (a prospective observational cohort study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes) to collect data about the presence or absence of drug-associated adverse developmental effects when SKLICE is used during pregnancy. This data could be used in pregnancy labeling to inform clinician and patient decision making regarding use of the product. SKLICE will likely be used by pregnant women as many of these women are exposed to lice via other children in the household.

SKLICE pregnancy labeling should be similar to Stromectol pregnancy labeling as the Sponsor is relying on the (b) (4) inform SKLICE pregnancy labeling. SKLICE pregnancy labeling should include the correct pregnancy category C regulatory language as Stromectol pregnancy labeling lacks the required pregnancy category C regulatory language. In addition, the SKLICE pregnancy subsection should be formatted as recommended above in the discussion section of this review.

PMHS-Maternal Health Team would be happy to assist with SKLICE pregnancy labeling revisions if so requested by DDDP.

**APPENDIX A:  
FDA Pregnancy Category Definitions**

<b>Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)</b>	
<b>Category</b>	<b>Definition</b>
<b>A</b>	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
<b>B</b>	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
<b>C</b>	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
<b>D</b>	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
<b>X</b>	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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

JEANINE A BEST  
07/19/2011

Karen B FEIBUS  
07/19/2011

I concur with the information presented and conclusion reached in this review.

LISA L MATHIS  
07/19/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 202736 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Sklice Established/Proper Name: ivermectin Dosage Form: Cream Strengths: 0.5%		
Applicant: Topaz Pharmaceuticals Inc. Agent for Applicant (if applicable):		
Date of Application: April 7, 2011 Date of Receipt: April 7, 2011 Date clock started after UN:		
PDUFA Goal Date: February 7, 2012	Action Goal Date (if different):	
Filing Date: June 6, 2011	Date of Filing Meeting: May 24, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3, 5 (new dosage form; new formulation or new manufacturer, same or new indication)		
Proposed indication(s)/Proposed change(s): Topical treatment of head lice <span style="background-color: #cccccc; padding: 0 5px;">(b) (4)</span> in patients 6 months and older		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>		
<i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 073134				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input checked="" type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th data-bbox="203 1446 495 1486">Application No.</th> <th data-bbox="495 1446 771 1486">Drug Name</th> <th data-bbox="771 1446 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1446 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at:  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	NA- electronic submission

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			A partial waiver of the requirement to submit pediatric assessments with

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

				respect to the pediatric population under 6 months of age was requested.
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Proprietary name "Sklice" was conditionally approved under the IND 073134.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			PMHS consulted- Maternal Staff consulted for change of pregnancy category, and Pediatrics Staff consulted to determine adequacy

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

				of pediatric safety database
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> August 12, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> February 18, 2011- The sponsor elected not to have their Pre-NDA meeting after receiving our draft Pre-Meeting Communication. They said that no further discussion was necessary. <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> December 23, 2009 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 18, 2011

**NDA #:** 202736

**PROPRIETARY NAME:** Sklice

**ESTABLISHED/PROPER NAME:** ivermectin

**DOSAGE FORM/STRENGTH:** Cream, 0.5%

**APPLICANT:** Topaz Pharmaceuticals

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

**BACKGROUND:** The studies to support the approval of this NDA were conducted under IND 073134. Pre-NDA Final Responses were communicated to the sponsor on January 12, 2011. An End-of-Phase 2 Meeting was held on August 12, 2009. On December 23, 2009, a Special Protocol Agreement Letter was issued to the sponsor.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Dawn Williams	Y
	CPMS/TL:	BJ Gould	Y
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom		Y
Clinical	Reviewer:	Jane Liedtka	Y
	TL:	Jill Lindstrom	Y
Clinical Pharmacology	Reviewer:	Chinmay Shukla	Y
	TL:	Doanh Tran	Y
Biostatistics	Reviewer:	Carin Kim/Xin Fang	Y
	TL:	Mohamed Alosh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jianyong Wang	Y

	TL:	Barbara Hill	Y
Product Quality (CMC)	Reviewer:	Caroline Strasinger	Y
	TL:	Shulin Ding	Y
Other attendees	Susan Walker Stephen Wilson		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> None</p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<i>mitigation, treatment or prevention of a disease</i>	
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIostatISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b> Instead of including Biostatistics issues in the 74-Day Letter, an IR will be sent to the sponsor immediately.</p>	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b> An IR item was included in the 74-Day Letter.</p>	

<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Divisional</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p>

	<p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DAWN WILLIAMS  
06/07/2011

BARBARA J GOULD  
06/07/2011

## DSI CONSULT: Request for Clinical Inspections

**Date:** May 20, 2011

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Jane Liedtka, MD, Clinical Reviewer, DDDP  
Jill Lindstrom, MD, Clinical Team Leader, DDDP

**From:** Dawn Williams, BSN, Regulatory Project Manager, DDDP

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA 202736

Applicant/ Applicant contact information (to include phone/email):

Topaz Pharmaceuticals

Contact: Lisa DeLuca, PhD, Vice President Regulatory Affairs

100 Witmer Rd

Suite 280

Horsham, PA 19044

Tel.: 267-960-3330

Fax: 267-960-3331

Email: [Lisa\\_DeLuca@topazpharm.com](mailto:Lisa_DeLuca@topazpharm.com)

Drug Proprietary Name: Sklice

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of head lice (b) (4) in patients 6 months of age and older

PDUFA: February 7, 2012

Action Goal Date: January 25, 2012

Inspection Summary Goal Date: November 25, 2011

DSI Consult

version: 5/08/2008

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 5 Cactus Kids Pediatrics 1832 South 8 <sup>th</sup> Ave. Yuma, AZ 85364 Contact: Claudia Carbajal Tel.: 928-782-6830 Fax: 928-782-3312 Email: (b) (6)	TOP011	Enrolled: 410 Completed: 406	Treatment of head lice (b) (4) in patients 6 months of age and older
Site 5 Lice Solutions 604 Gallatin Ave. #105 Nashville, TN 37206-3476 Contact: Abby Irwin Tel.: 615-227-3919 Fax: 615-227-3920 Email: abby@liceresolutions.org	TOP012	Enrolled: 371 Completed: 359	Treatment of head lice (b) (4) in patients 6 months of age and older
Site 6 Universal Biopharma Research, Inc. 888 N. Alta Ave. Dinuba, CA 93618 Contact: Roberto Manzanedo Tel.: 559-595-1861 Fax: 559-595-1851 Email: (b) (6)	TOP011	Enrolled: 410 Completed: 406	Treatment of head lice (b) (4) in patients 6 months of age and older

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 3 Lice Solutions 6758 N. Military Trail Suite H West Palm Beach, FL 33407 Contact: Gina Pierce Tel.: 561-842-9969 Fax: 561-842-0311 Email: gina@licesolutions.org	TOP011	Enrolled: 410 Completed: 406	Treatment of head lice (b) (4) in patients 6 months of age and older

**III. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

***Rationale for DSI Audits***

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See\*\*\* at end of consult template for DSI's thoughts on things to consider in your decision making process*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): the largest delta was noted at sites #5 (TOP011, TOP012)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Site #6 in TOP011 enrolled 20 subjects rapidly under the central randomization scheme\* and then only an additional 4 subjects once the randomization changed to by site\*, in addition this site had a very high efficacy rate for the control group
- Other (specify): Site #3 in TOP011- this site had a significant change in the treatment effect after the change in the randomization scheme was instituted\*

\*randomization (according to the SPA letter-dated 12/23/09) was planned to be stratified by site. However, randomization was centralized from study onset thru till April 16, 2010 when this error was identified and corrected by the sponsor. We have an IR pending to get more details on this error.

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact Dawn Williams at 301-796-5376, or Jane Liedtka at 301-796-0517.



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DAWN WILLIAMS  
05/24/2011