# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022408Orig1s000

# OTHER REVIEW(S)

# SEALD LABELING: PI SIGN-OFF REVIEW

| | |
|---|---|
| APPLICATION NUMBER | NDA 22-408 |
| APPLICANT | Parapro Pharmaceuticals, LLC |
| DRUG NAME | NATROBA (spinosad) topical suspension, 0.9% |
| SUBMISSION DATE | 26 July 2010 |
| PDUFA DATE | 26 January 2011 |
| SEALD SIGN-OFF DATE | 12 January 2011 |
| OND ASSOCIATE DIRECTOR FOR LABELING | Laurie Burke |

This memo confirms that all critical prescribing information (PI) deficiencies found in the SEALD Labeling Review filed 17 December 2010 for this application have been addressed. I reviewed the final agreed-upon PI and agree that it meets the regulatory requirements found in 21 CFR 201.56 and 57 and is ready for approval at this time.

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/s/

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LAURIE B BURKE
01/12/2011

# SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

| | |
|---|---|
| APPLICATION NUMBER | NDA 022408 |
| APPLICANT | Parapro Pharmaceuticals, LLC |
| PRODUCT NAME | Natroba (spinosad) |
| SUBMISSION DATE | July 26, 2010 |
| PDUFA DATE | January 26, 2011 |
| SEALD REVIEW DATE | December 17, 2010 |
| SEALD LABELING REVIEWER | Debra Beitzell, BSN/Ann Marie Trentacosti.MD |

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

# Selected Requirements for Prescribing Information

For other regulatory requirements, see 21 CFR 201.56 and 201.57.

## Highlights (HL)

- **General comments**
  - ☐ Highlights is in 8-point font, two-column format, with ½ inch margins.
  - ☐ Highlights is limited in length to one-half page. If greater than one-half page, a waiver has been granted previously or has been 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 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. The cross reference number under the Adverse Reactions heading should be 6.1, not 6.
  - ☐ Includes the following headings in the following order:

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

- **Highlights Limitation Statement**
  - ☐ Must be **bolded** and placed at the beginning of Highlights and read as follows: "**These highlights do not include all the information needed to use [insert name of drug product in UPPER CASE] safely and effectively. See full prescribing information for [insert name of drug product in UPPER CASE]**."

- **Product Title**
  - ☐ Must be **bolded** and include the proprietary and nonproprietary drug names, followed by the drug's dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ Must include the 4-digit year of the initial U.S. approval of the new molecular entity (NME), new biological product, or new combination of active ingredients. If this is an NME, the year corresponds to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary 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 Highlights boxed warning is identical to FPI boxed warning, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each labeling section affected by the change must be listed with the date (MM/YYYY format) 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 in HL 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."

- **Indications and Usage**

  ☐ If a product is a member of 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 heading must be included in HL and not 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). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and cross-reference to Contraindications section (4).

- **Warnings and Precautions**

  ☐ Pregnancy Category D drugs have positive human risk findings. These findings must be noted as a warning. Therefore, must state the following: “Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus.”

- **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,” cannot be used. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%). The review team determined that the adverse reactions could not be adequately differentiated from the adverse events based on information included in the prescribing information.

  ☐ 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**” must be present. Only include a toll free number.

- **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 will be the month/year of application or supplement approval. Insert the revision date in "MM/YYYY" format upon approval.

## Contents: Table of Contents (TOC)

☒ The heading – **FULL PRESCRIBING INFORMATION: CONTENTS** – must appear at the beginning of the TOC in UPPER CASE and **bold** type. Heading must be bolded.

☒ The headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI. Subsection number 6.1 and heading is missing from TOC; please insert.

☒ All section headings must be in **bold** type, and subsection headings must be indented and not bolded. Bold section number "8."

☐ 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)

☐ When 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 the Contents: "*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. Heading must be bolded.

☐ 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 summary.

☐ Must include a brief, concise summary of critical information and cross-reference to more detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

  ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Warnings and Precautions**

  ☐ For Pregnancy Category D drugs, list pregnancy as a Warning and Precaution.

- **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," cannot be used. The review team determined that the adverse reactions could not be adequately differentiated from the adverse events.

  ☒ For the "Clinical Trials Experience" subsection, the following verbatim statement 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." Throughout paragraph replace "studies" with "clinical." Also, insert "clinical" before "practice" at end of paragraph.

  ☐ For the "Postmarketing Experience" subsection, the listing must be separate from the listing of adverse reactions identified in clinical trials and include the following verbatim statement:

  - "The following adverse reactions have been identified during post approval use of drug X. 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 are required.

- **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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ANN M TRENTACOSTI
12/17/2010

**Attachment B: PMC Development Template**

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

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PMR/PMC Title: PK Study in Subjects 6 Months to 4 Years of Age with Active Head Lice Infestation

PMR/PMC Schedule Milestones:
Protocol Submission Date: March (b)(4), 2011
Study Initiation Date: September (b)(4) 2011
Study Completion Date: December (b)(4), 2011
Final Study Report Submission Date: March (b)(4), 2012
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

| |
|---|
| Studies already completed in subjects 4 years of age and older indicate safety and efficacy. |

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
***If not a PMR, skip to 4***.

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☒ Pediatric requirement
  - ☐ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

| |
|---|
| Maximal use pharmacokinetic trials were conducted and detected no systemic exposure of spinosad from the use of Natroba™ (spinosad) Suspension, 0.9%. However, only 8 healthy subjects under the age of 4 years were evaluated. For topically applied products, bioavailability testing must be accomplished in subjects with the disease of interest. This is the basis of the need for PK information from subjects, having active head lice infestations, 6 months to 4 years of age. Since the product also contains benzyl alcohol, PK information will be obtained on both spinosad and benzyl alcohol. Benzyl alcohol levels have not been determined to date in any of the subjects enrolled in this NDA |

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. What type of study or clinical trial is required or agreed upon (describe)?

The study would be an open label PK study of Natroba Suspension under maximum use conditions in subjects age 6 months to 4 years, with a minimum of 24 evaluable subjects divided by age into a group 6 months to 2years and a group 2 to 4 years with a roughly equal distribution of ages and gender in both groups. Safety evaluation would be included in the study design for both local and systemic safety. Subjects would otherwise be healthy, except for active lice infestation. The primary pharmacokinetic analysis of spinosad and of benzyl alcohol is to include a determination of the following parameters: single dose AUC, $C_{max}$, and $T_{max}$.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

_____

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

_____

☐ Subpopulation (list type)

_____

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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**CDTL or PMR/PMC Development Coordinator:**
*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.* ☐

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/s/

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DAWN WILLIAMS
11/26/2010

TATIANA OUSSOVA
11/26/2010

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | October 29, 2010 |
| To: | Susan Walker, MD, Director<br>Division of Dermatology and Dental Products |
| Through: | Kristina A. Toliver, PharmD, Team Leader<br>Denise P. Toyer, PharmD, Deputy Director<br>Carol A. Holquist, RPh, Director<br>Division of Medication Error Prevention and Analysis (DMEPA) |
| From: | Loretta Holmes, BSN, PharmD, Safety Evaluator<br>Division of Medication Error Prevention and Analysis (DMEPA) |
| Subject: | Label and Labeling Review |
| Drug Name: | Natroba (Spinosad) Suspension<br>0.9% |
| Application Type/Number: | NDA 022408 |
| Applicant: | ParaPRO Pharmaceuticals, LLC |
| OSE RCM #: | 2010-1634 |

# Contents

# 1 INTRODUCTION

This review responds to a request from the Division of Dermatology and Dental Products for DMEPA's assessment of the revised container label and carton labeling of Natroba (Spinosad) suspension 0.9%.

The container label, carton and insert labeling were previously reviewed in OSE Review 2009-328.

# 2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) when evaluating container labels, carton and insert labeling. This review summarizes our evaluation of the container label, carton and insert labeling submitted by the Applicant on July 23, 2010 (see Appendices A and B for images of the container label and carton labeling).

# 3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. Specifically, we have concerns with the Dosage and Administration section, Warnings and Precautions, and route of administration statement.

Additionally, we note the Applicant did not address all of the recommendations from our previous label and labeling review (OSE Review 2009-328). We met with the Division on October 5, 2010 to discuss our recommendations for the Dosage and Administration, Warnings and Precautions, and route of administration portions of the container label and carton labeling in order to come to a consensus. Thus, those recommendations that were not followed and still needed to be addressed were included in our recommendations that were communicated to the Applicant via email on October 8, 2010 (see Appendix A).

We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the review team's label and labeling meetings.

We would be willing to meet with the Division for further discussion, if needed. 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, please contact Janet Anderson, OSE Regulatory Project Manager, at 301-796-0675.

## 3.1 COMMENTS TO THE DIVISION

Patient Information section of the Insert Labeling

We note the Patient Instructions for Use section of the insert labeling submitted by the Applicant on July 23, 2010 provide little detail for patients about the correct use of Natroba. However, we acknowledge the Division's working copy of the Insert provides more comprehensive instructions in the Patient Instructions for Use. The working copy addresses our concerns, therefore, we have no additional comments on the Patient Instructions for Use section of the insert labeling.

## APPENDICES

**Appendix A:** Label and Labeling Recommendations Communicated to the Applicant on October 8, 2010.

Container Label and Carton Labeling

1. The statement "(b) (4) contains terms that refer to product mechanism of action which do not belong on the container label and carton labeling. Delete the statement (b) (4) since these terms may be confusing, unfamiliar to patients, and not meaningful in terms of what patients need to know in order to use the product correctly. Additionally, this is not information that healthcare providers need to know when handling or dispensing the product. The mechanism of action is provided in the insert labeling for healthcare providers who need to know this information.
2. The route of administration (i.e., "For topical use only") is not on the principal display panel. Ensure the route of administration statement is displayed prominently on the principal display panel and positioned below the product identifying information (i.e., proprietary name, established name, dosage form, and strength). Additionally, modify the statement to read "For topical use on the scalp hair and scalp only." This will help to prevent use of the product on other areas of the body.
3. (b) (4) Therefore, revise the Usual Dosage statement as follows: "See package insert, including the patient information section, for full prescribing and dosing information."
4. Revise the Warnings and Precautions as follows. Revise the title to "Warnings". Delete the following statements:

(b) (4)

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/s/

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LORETTA HOLMES
10/29/2010

KRISTINA C ARNWINE
10/29/2010

DENISE P TOYER
10/29/2010

CAROL A HOLQUIST
11/02/2010

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

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

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# CLINICAL INSPECTION SUMMARY

DATE: October 16, 2009

TO: Catherine Carr, Regulatory Project Manager
Patricia Brown, M.D., Medical Officer
Division of Reproductive and Urologic Drugs Products

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

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-408

APPLICANT: ParaPRO Pharmaceuticals, LLC.

DRUG: TRADENAME (spinosad) (b) (4)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of head lice

CONSULTATION REQUEST DATE: April 27, 2009

DIVISION ACTION GOAL DATE: November 22, 2009

PDUFA DATE: November 22, 2009

## I. BACKGROUND:

The conduct of Protocols #SPN-301-07 and #SPN-302-07, both entitled "A Comparative Safety And Efficacy Study Between Natrova Creme Rinse 1 % And Nix Creme Rinse In Subjects ≥ 6 Months Of Age With *Pediculosis Capitis*" was inspected.

For both studies, the primary efficacy endpoint was the proportion of primary subjects that were lice free 14 days after the last application of the drug product (i.e., Day 14 for those subjects with one application, and Day 21 for those with two applications). The secondary endpoint was the proportion of subjects (primary and non-primary subjects) within each treatment group requiring two treatments.

The primary objective of these studies was to demonstrate the efficacy of NatrOVA® 1% Creme Rinse relative to NIX® Creme Rinse under "actual use" conditions in subjects who were infested with *Pediculosis capitis.*

The clinical sites of Drs. Haber, Moore, and Stough and Ms. Shepherd were selected for inspection because Dr. Haber's site had the largest treatment effect – 100% success rate for the sponsor's product without nit combing arm compared to a very low success rate (12.5%) for the NIX® arm. Dr. Moore's site was selected for a similar reason (100% with nit combing compared to a 21.4% success rate of NIX®), and also because the success rates for both the sponsor's product arms (with combing and without combing) had 100% treatment success. Dr. Stough's site was selected because it had the largest enrollment (52 subjects) and also because the sponsor's product arm with nit combing arm had a lower response rate compared to that of the without nit combing arm. Typically, a higher success rate is expected with nit combing; therefore, it is unusual that the success rate was higher without nit combing. Ms. Shepherd's site was selected because it had the largest enrollment (52 subjects) with large treatment effects. Sites were also selected on the basis of representation from different areas of the country due to geographic variations in louse resistance to known treatments.

## II. RESULTS (by Site):

| Name of CI, Location | Protocol #/ # of Subjects/ | Inspection Dates | Final Classification |
|---|---|---|---|
| **Site 03**<br>Robert S. Haber, M.D.<br>Haber Dermatology<br>14077 Cedar Rd, Suite 200<br>South Euclid, OH. 44118<br>(216) 932-5200 | SPN-301-07/<br>19/ | 15-18 Jun 2009 | NAI |
| **Site 07**<br>Mark L. Moore, M.D.<br>Concentrics Center for Research<br>9325 Delegates Row<br>Indianapolis, IN. 46240<br>(317)706-3222 | SPN-302-07/<br>32/ | 22-24 Jun 2009 | VAI |
| **Site 05**<br>Dow B. Stough, M.D., C.C.T.I.<br>Burke Pharmaceutical Research<br>3633 Central Ave., Suite I<br>Hot Springs, AK. 71913<br>(501)620-4449 | SPN-301-07/<br>54/ | 21-24 Jul 2009 | VAI. |
| **Site 09**<br>Katie Shepherd, B.A., P.A.<br>Lice Solutions Research Network<br>6758 N. Military Trail, Suite 110<br>West Palm Beach, FL. 33407<br>(561)84209969 | SPN-302-07/<br>54/ | 17-20 Aug 2009 | 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 on 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Robert S. Haber, M.D.
   Haber Dermatology
   14077 Cedar Rd, Suite 200
   South Euclid, OH. 44118
   (216) 932-5200

   **a. What was inspected**: The records of the 38 subjects randomized to the study were audited. Records reviewed included, but were not limited to, eligibility verification, primary efficacy and safety endpoints, adverse events, concomitant medications, and test article accountability. Source documents were compared and verified against case report forms and line 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/regulatory violations.

**c. Assessment of data integrity**: Data appear acceptable in support of the respective application.

2. Mark L. Moore, M.D.
   Concentrics Center for Research
   9325 Delegates Row
   Indianapolis, IN. 46240
   (317)706-3222

   **a. What was inspected**: At this site, 100 subjects were enrolled in the study with 96 subjects completing the study. The records for 28 of the 32 families involved were reviewed. Other records reviewed included, but were not limited to, Informed Consent Forms (ICFs), sponsor correspondence, Case Report Forms (CRFs), source documentation, inclusion/exclusion criteria, randomization schedules, drug accountability records, IRB correspondence, laboratory reports, concomitant medication records, and adverse events records.

   **b. General observations/commentary**: A Form FDA 483 was issued stating that for the first 14 families enrolled in the study there were no informed consent forms (ICFs) containing the names of children under 12 years of age and signed by a parent/guardian. Further review indicated that families were enrolled and consented as a household unit because of the nature of the study. This household consent process was not in compliance with applicable regulations regarding the documentation of informed consent, although it appears that informed consent was obtained verbally.

   **c. Assessment of data integrity:** Though the informed consent process was not compliant with applicable regulations, it would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

3. Dow B. Stough, M.D.
   Burke Pharmaceutical Research
   3633 Central Ave., Suite I
   Hot Springs, AK. 71913
   (501) 620-4449

   **a. What was inspected**: At this site, 186 subjects were screened, 164 subjects were enrolled and 159 subjects completed the study. The records of 22 of the 54 families were reviewed. Documentation reviewed included, but was not limited to, Informed Consent Forms (ICFs), Case Report Forms (CRFs), source documentation, inclusion/exclusion criteria, drug accountability records, IRB correspondence, concomitant medication records, and adverse events records.

**b. General observations/commentary**: A Form FDA 483 was issued noting a problematic assent process, delayed signatures on consent forms for four subjects, a lack of documentation of minor adverse events in a small subset of subjects, and an example of inadequate documentation of concomitant medication for one subject. Dr. Stough responded satisfactorily in writing in a letter dated July 27, 2009, to the observations on the Form FDA 483.

c. **Assessment of data integrity:** Neither the problematic consent and assent issues or the lack of documentation of minor adverse events (a generally transient increase in scalp irritation score of one unit), and record keeping errors regarding minor discrepancies in drug dosing would appear to have a significant effect on data integrity. The data generated by this site may be used in support of the respective indication.

4. Katie Shepherd, B.A., P.A.
   Lice Solutions Research Network
   6758 N. Military Trail, Suite 110
   West Palm Beach, FL. 33407
   (561) 842-09969

**a. What was inspected**: At this site, 274 subjects from 69 households were screened, with 143 subjects that enrolled and completed the study. The records of 32 subjects were reviewed. Documentation reviewed included, but was not limited to, informed consent forms, source documents and corresponding case report forms, IRB and sponsor correspondence, and drug accountability records.

**b. General observations/commentary**: A Form FDA 483 was not issued at the conclusion of this inspection. Review of the records noted above revealed no significant discrepancies/regulatory violations.

**c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

## III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical sites were inspected in support of this application. The data generated by the clinical sites of Drs. Haber, Moore, and Stough, and Ms. Shepherd appear acceptable in support of the respective application.

*{See appended electronic signature page}*

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

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ROY A BLAY
10/16/2009

TEJASHRI S PUROHIT-SHETH
10/16/2009

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

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
FAX 301-796-9744

# Pediatric and Maternal Health Staff Review

**Date:** October 6, 2010 **Date Consulted:** August 17, 2010

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

**Through:** Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Karen B. Feibus, M.D., Team Leader – Maternal Health Team
Pediatric and Maternal Health Staff

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

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

**Drug:** Natroba ™ (spinosad) Suspension, 0.9% USP, NDA 22-408

**Subject:** Pediatric Use, Pregnancy, and Nursing Mothers Labeling; Benzyl Alcohol Warnings

**Materials Reviewed:**

- Sponsor CR Resubmission, July 26, 2010
- DDDP Clinical Review, October 16, 2010
- DDDP Division Director Summary Review
- ODE III Director Review, November 18, 2001
- DDDP Clinical Pharmacology Review, October 6, 2010
- DDDP Pharmacology/Toxicology Review, August 20, 2009

**Consult Question:** Please review the pediatric use, pregnancy, and nursing mothers subsections of labeling (product contains benzyl alcohol).

## INTRODUCTION

ParaPro Pharmaceuticals, LLC submitted a new Drug Application (NDA 22-408) on January 21, 2009, for Natroba (spinosad) Suspension, 0.9%, for the treatment of head lice infestations. FDA issued a Complete Response on November 18, 2009, for unresolved active ingredient issues, outstanding CMC issues, and inadequate pharmacokinetic data to support use in children under 4 years of age. A Complete Response submission was submitted on July 23, 2010.

ParaPro Pharmaceuticals, LLC was seeking a head lice treatment indication (b) (4)

Pharmacokinetic data, for safety reasons, is needed in young children with head lice to determine the effect of the condition on drug absorption for inflamed skin. The Sponsor's current pediatric plan to address the Pediatric Research Equity Act (PREA) does not explain how or when they plan to conduct required pediatric studies in patients ages 6 months to less than 4 years of age. The current pediatric plan only includes a waiver request for studies in patients under 6 months of age.

*Reviewer comment: The Sponsor must submit a pediatric plan outlining the studies they plan to conduct, along with a timeline for completion of these studies, including the date the protocol will be submitted, the date studies will be completed and the date the final study report(s) will be submitted. The studies must be sufficient to demonstrate dose, safety and efficacy for the 6 mo to 4 year old age group.*

The Division of Dermatology and Dental Products (DDDP) consulted PMHS-Pediatric Team on August 16, 2010, and the PMHS-Maternal Health Team (MHT) on August 25, 2010, to review the proposed Pediatric Use, Pregnancy, and Nursing Mothers subsections of labeling.

This review provides PMHS's suggested revisions to the sponsor's proposed Pediatric Use, Pregnancy, and Nursing Mothers subsection of labeling, as well as adding the appropriate benzyl alcohol toxicity warnings for neonates and infants. PMHS labeling edits will be added to Natroba labeling in the DDDP e-room as requested.

## BACKGROUND

### Spinosad

Natroba (spinosad) Suspension, 0.9%, is a topical drug product that contains the active ingredient spinosad (spinocyn A and spinocyn D, naturally-derived fermentation products produced by an actinomycete) and benzyl alcohol (b) (4) for spinosad. Spinosad is also used as an agricultural pesticide. The Sponsor conducted pk studies with the active ingredient spinosad, in patients 4years and older, and no detectable systemic absorption was demonstrated with the assay method used.

Benzyl alcohol has demonstrated effectiveness in treating head lice, but not lice ova. A 5% benzyl alcohol active ingredient product (Ulesfia) was approved for the topical treatment of head lice on April 9, 2009. FDA has determined for Natroba that the (b) (4) benzyl alcohol is a formulation necessity (b) (4); and therefore, an inactive ingredient. The Sponsor did not

obtain pk data on the benzyl alcohol in Natroba; therefore, human systemic exposure from this higher concentration of benzyl alcohol and combination is unknown. Benzyl alcohol absorption was demonstrated with Ulesfia, particularly in younger pediatric patients.

**Benzyl Alcohol**

Benzyl alcohol is used in a variety of drug products (b) (4) In 1982, two groups of investigators independently concluded that intravascular infusion or flush solutions containing benzyl alcohol, 0.9% caused severe metabolic acidosis, encephalopathy, and respiratory depression with gasping, leading to the death of 16 infants in neonatal intensive care units. This conclusion was based on the discovery of large amounts of benzyl alcohol and its metabolites, benzoic acid and hippuric acid, in the blood and urine of the affected neonates. The benzyl alcohol amounts found in the deceased neonates were in the lethal range for laboratory animals.[1,2] The minimum amount of benzyl alcohol at which toxicity may occur is not known; however, severe toxicities and death in infants were associated with benzyl alcohol dosages >99 mg/kg/day.

In May 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a bulletin containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.[3]

Benzyl alcohol toxicity occurs in infants, particularly in low birth-weight infants, because greater amounts of benzyl alcohol are received relative to body weight, and the infants' metabolic and excretory pathways are still immature.[4]

PMHS has developed standard benzyl alcohol toxicity warning language for drug product labeling of products that contain benzyl alcohol. This warning, or in some instances, a contraindication, is directed at use of benzyl alcohol-containing products in neonates and infants. At times, depending on amount of benzyl alcohol systemic exposure, the warning is also directed at pregnant and lactating women because exposure to benzyl alcohol can occur via the placenta or human milk.

**Pediatric Research Equity Act (PREA)**

The Pediatric Research Equity Act (PREA), originally enacted on December 3, 2003 (Public Law 108-155), codified many of the elements of the Pediatric Rule (63 FR 66632), in particular the requirement for pediatric studies of certain drugs and biological products used in pediatric patients. PREA was reauthorized by FDAAA, as Title IV, on September 27, 2007. Specifically, PREA 2007 [section 505B of the Act (21 U.S.C. 355c)] requires new drug applications (NDAs)

[1] Gershanik J, Boecler B, Ensley H, et al. The gasping syndrome and benzyl alcohol poisoning, NEJM. 1982;301:1384

[2] Brown W, Buist N, Gipson H, et al. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. Lancet. 1982;1:1250

[3] American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. Pediatrics. 1983;72(3):356-8

[4] Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. 1986;77(4):500-6

and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act).

**Pediatric Labeling**

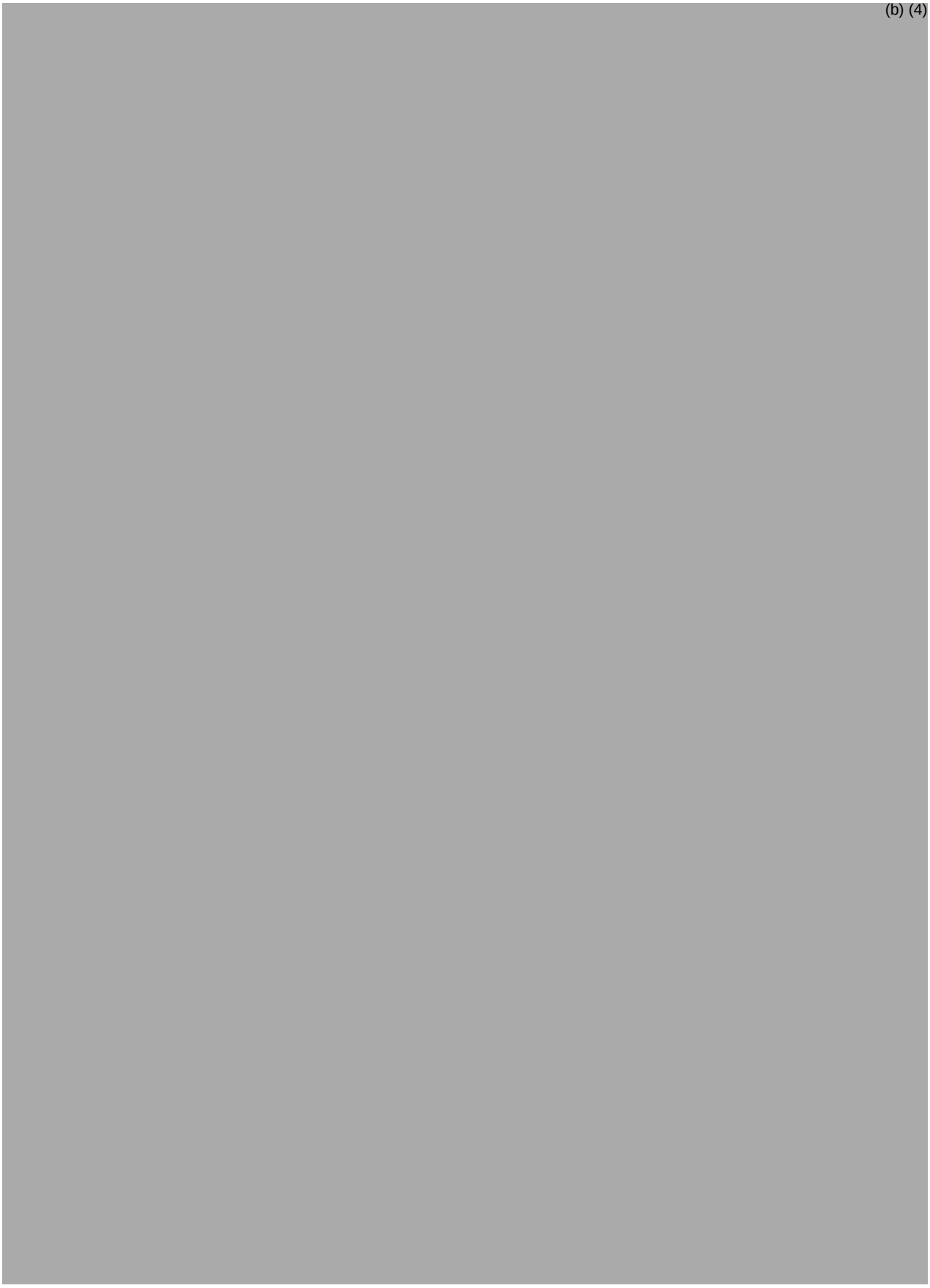
The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

**Pregnancy and Nursing Mothers Labeling**

Until the PLLR publishes, the Maternal Health Team has developed a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations, including the assignment of pregnancy categories, but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount, as this can vary significantly from species to species.

**SUMBMITTED SPONSOR LABELING (WITH DDDP EDITS, AUGUST 26, 2010)**

(b) (4)


(b) (4)

(b) (4)

**DISCUSSION AND CONCLUSIONS**

DDDP consulted both the PMHS-Pediatric Team and PMHS-Maternal Health Team to comment on the proposed labeling for Natroba Suspension, a product that contains (b) (4) benzyl alcohol (b) (4) for the active ingredient spinosad. Pharmacokinetic (pk) studies conducted in patients 4 years and older with head lice showed no detectable systemic absorption of spinosad with the assay method used. These pk studies did not assess for the absorption of benzyl alcohol; important data that could have better informed use in children and women who are pregnant or breastfeeding, as systemic exposure to benzyl alcohol is expected. More importantly, pk studies conducted in pediatric patients, ages 6 months to 4 years of age, were conducted in healthy children without head lice, a study that cannot be used to inform pediatric clinical use of Natroba Suspension, and one that raises ethical concerns. The Sponsor submitted a required pediatric plan that only requests a waiver for pediatric patients under 6 months of age and that does not address studies in the 6 months to less than 4 years of age pediatric age group. A pediatric plan must address and outline studies which are adequate for determining dosing, safety and efficacy in all pediatric age groups for a drug product that triggers PREA (see section 505B(a) of the Act). The pediatric plan must also include a timeline for the conduct of the studies.

Benzyl alcohol is used in a variety of cosmetic skin products and hair dyes (b) (4) . Based on the available data from toxicity, mutagenicity, carcinogenicity, reproductive/developmental, and sensitization studies, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that benzyl alcohol is safe for use in cosmetic formulations at concentrations up to 5%, and in hair dyes at concentrations up to10% (hair dye use involves limited body area exposure, has a controlled exposure time per use, and has limited frequency of use).[5]

PMHS has developed standard pediatric use language warning against the use of benzyl alcohol-containing products in neonates and infants, as the amount of systemically available benzyl alcohol that can lead to toxicity in these age groups is unknown. In addition the warning against using benzyl alcohol-containing products in neonates and infants usually applies to pregnant and lactating women, as the amount of benzyl alcohol that a fetus would receive via the placenta, or that a human milk-fed infant would receive from breast milk are unknown. The warning is not

[5] Final Report on the Safety Assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. International Journal of Toxicology; 2001 Supplement 3, Vol. 20, p23-50, 28p

necessary for Natroba Suspension because the product is usually administered as a single treatment (occasionally a repeat treatment is required) and fetal (via the placenta) and infant exposure (via human milk) is expected be minimal and probably comparable to the systemic absorption that occurs with hair dye use. In addition, a lactating woman who uses the product can choose to and pump and discard breast milk for five half-lives of benzyl alcohol, in order to avoid any infant ingestion of benzyl alcohol from Natroba Suspension.

**CONCLUSIONS**

PREA requires the Sponsor to provide an assessment of Natroba suspension in all pediatric age groups. The Sponsor has submitted a waiver for studies in pediatric patients less than six months of age because there are too few patients with the condition to study in this age group; however, there is also a safety concern because of a potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the possibility for an immature skin barrier in this age group. Therefore, labeling must reflect the safety concern. The Sponsor is required to submit an updated Pediatric Plan that includes a deferral request along with a description of the proposed studies of Natroba suspension in pediatric patients 6 months to less than 4 years of age. This plan must include a timeline with specific dates for protocol submission, study date completion and final report submission. The pk study conducted in healthy patients ages 6 months to less than 4 years of age, which raises ethical concerns (it exposed children who could not derive direct benefit from the drug, to more than minimal risk cannot be used to support safety for an indication in this age group. The complete Pediatric Plan must be submitted prior to approval of this Natroba suspension NDA. Any deferred pediatric study will be considered a required pediatric postmarketing study and when submitted for review to the Agency must be clearly designated as "Required Pediatric Assessment".

Natroba suspension labeling should be revised to include the appropriate benzyl alcohol toxicity warning for neonate and infants. Information regarding the presence of benzyl alcohol in Natroba Suspension should be included for pregnant and lactating women since systemic exposure is expected and pharmacokinetic studies did not assess for the absorption of benzyl alcohol. Labeling should also describe ways for nursing mothers to minimize benzyl alcohol exposure via human milk ingestion.

**PMHS RECOMMENDATIONS**

1. Notify the Sponsor that they are required to submit an updated Pediatric Plan that includes the deferral request and proposed pediatric studies of Natroba Suspension in pediatric patients 6 months to less than 4 years of age prior to product approval. The plan must include timelines with specific dates.

2. Request pharmacokinetic data on both spinosad and benzyl alcohol in the deferred study in pediatric patients with head lice 6 months to less than 4 years of age.

3. Notify the Sponsor that any deferred pediatric study will be considered a required pediatric postmarketing study and when submitted for review to the Agency must be clearly designated as "Required Pediatric Assessment".

**Labeling Recommendations**
Provided below are the PMHS recommended pediatric use, pregnancy, and nursing mothers labeling revisions for Natroba Suspension, as well as the benzyl alcohol toxicity warning language neonates and infants. These revisions were discussed with DDDP at a labeling meeting held on September 30, 2010.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**----------INDICATIONS AND USAGE----------**
Natroba™ Suspension is a pediculocide indicated for the topical treatment of head lice infestations in patients 4 years of age and older. (1.1)

**----------WARNINGS AND PRECAUTIONS----------**
- Benzyl alcohol toxicity: Risk of serious adverse events and death, particularly in neonates and low birth-weight infants (5.1)

**----------USE IN SPECIFIC POPULATIONS----------**
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: Not recommended in pediatric patients below the age of 6 months; potential for increased systemic absorption. Safety in pediatric patients below the age of 4 years has not been established.(8.4)

**1 INDICATIONS AND USAGE**
1.1 Indication
Natroba Suspension is indicated for the topical treatment of head lice infestation in patients 4 years of age and older.

**5 WARNINGS AND PRECAUTIONS**
5.1Benzyl Alcohol Toxicity
Natroba Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse events and death, particularly in neonates and low birth-weight infants *[see Use in Specific Populations (8.4)]*.

**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
Pregnancy Category B
There are no adequate and well-controlled studies with Natroba Suspension in pregnant women. Studies in humans did not assess for the absorption of benzyl alcohol contained in Natroba Suspension. Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No comparisons of animal exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study *[see Clinical Pharmacology (12.3)]* which did not allow for the determination of human AUC values that could be used for this calculation.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 10, 50 and 200 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 200 mg/kg/day. Oral doses of 2.5, 10, and 50 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 7 – 19) to pregnant female rabbits. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 50 mg/kg/day.

A two-generation dietary reproduction study was conducted in rats. Oral doses of 3, 10, and 100 mg/kg/day spinosad were administered to male and female rats from 10-12 weeks prior to mating and throughout mating, parturition, and lactation. No reproductive/developmental toxicity was noted at doses up to 10 mg/kg/day. In the presence of maternal toxicity, increased dystocia in parturition, decreased gestation survival, decreased litter size, decreased pup body weight, and decreased neonatal survival occurred at a dose of 100 mg/kg/day.

8.3 Nursing Mothers

Spinosad, the active ingredient in Natroba Suspension is not systemically absorbed; and therefore, will not be present in human milk. However, Natroba Suspension contains benzyl alcohol, which is systemically absorbed through the skin, and the amount of benzyl alcohol excreted in human milk with use of Natroba Suspension is unknown. Caution should be exercised when Natroba™ Suspension is administered to a nursing woman. A nursing woman may choose to pump and discard breast milk for X hours (5 half-lives of benzyl alcohol) after use to avoid infant ingestion of benzyl alcohol. An infant may be fed previously stored human milk or formula during this time period.

*Reviewer Comment: The Clinical Pharmacology reviewer should provide the time for 5 half-lives of benzyl alcohol.*

8.4 Pediatric Use

The safety and effectiveness of Natroba Suspension have been established in pediatric subjects 4 years of age and older with active head lice infestation. *[See Clinical Studies (14)]*. Safety in pediatric patients below the age of 4 years has not been established.

Natroba Suspension should not be used in pediatric patients below the age of 6 months because of the potential for increased systemic absorption (of benzyl alcohol?)due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.

Natroba suspension contains benzyl alcohol which has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity *[see Warnings and Precautions (5.1)]*.

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JEANINE A BEST
10/06/2010

Karen B FEIBUS
10/06/2010
I agree with the discussion and labeling revisions presented in this review.

LISA L MATHIS
10/06/2010

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | September 28, 2010 |
| To: | Susan Walker, MD, Director<br>**Division of Dermatology and Dental Products (DDDP)** |
| Through: | LaShawn Griffiths, RN, MSHS-PH, BSN,<br>Patient Labeling Reviewer, Acting Team Leader<br>**Division of Risk Management** |
| From: | Steve L. Morin RN, BSN, OCN<br>Patient Labeling Reviewer<br>**Division of Risk Management** |
| Subject: | DRISK Review of Patient Labeling Patient Package Insert |
| Drug Name(s): | Natroba (spinosad) Suspension, 0.9% |
| Application Type/Number: | NDA 22-408 |
| Applicant/sponsor: | ParaPro Pharmaceuticals, LLC |
| OSE RCM #: | 2010-1845 |

## 1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Natroba (spinosad) Suspension 0.9% , for the topical treatment of head lice in patients four years of age and older. Please let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## 2 MATERIAL REVIEWED

- Natroba (spinosad) Suspension, 0.9% Prescribing Information (PI) submitted January 21, 2009 revised by the Review Division throughout the current review cycle and provided to DRISK on September 2, 2010.
- Natroba (spinosad) Suspension, 0.9% Patient Package Insert submitted on January 21, 2009 revised by the Review Division throughout the current review cycle and provided to DRISK on September 2, 2010.
- Ulesfia (benzyl alcohol) lotion Patient Package Insert

## 3 RESULTS OF REVIEW

In our review of the PPI we have:

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

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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STEVE L MORIN
09/28/2010
DRISK PPI Review

LASHAWN M GRIFFITHS
09/28/2010

# *MEMORANDUM*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

## **PRE-DECISIONAL AGENCY MEMO**

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**Date:** September 3, 2010

**To:** Dawn Williams, DDDP

**From:** Lynn Panholzer, PharmD, DDMAC
Sheetal Patel, PharmD, DDMAC

**Re:** NDA# 022408
Natroba™ (spinosad) Suspension, 0.9%

As requested in your consult dated August 19, 2010, DDMAC has reviewed the draft labeling for Natroba™ (spinosad) Suspension, 0.9%. DDMAC's comments are based on the proposed substantially complete, mark-up, version of the labeling accessed at http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0_191b0.

DDMAC's comments are provided directly in the attached marked-up copy of the labeling.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at 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.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22408 | ORIG-1 | PARAPRO PHARMACEUTICALS LLC | SPINOSAD |

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/s/

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LYNN M PANHOLZER
09/03/2010

SHEETAL PATEL
09/07/2010

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | November 5, 2009 |
| To: | Susan Walker, MD, Director<br>Division of Dermatology and Dental Products |
| Through: | Kristina C. Arnwine, PharmD, Team Leader<br>Denise P. Toyer, PharmD, Deputy Director<br>Carol A. Holquist, RPh, Director<br>Division of Medication Error Prevention and Analysis (DMEPA) |
| From: | Loretta Holmes, BSN, PharmD, Safety Evaluator<br>Division of Medication Error Prevention and Analysis (DMEPA) |
| Subject: | Label and Labeling Review |
| Drug Name: | (b) (4) (Spinosad) Suspension 0.9% |
| Application Type/Number: | NDA 22408 |
| Applicant: | ParaPRO Pharmaceuticals, LLC |
| OSE RCM #: | 2009-328 |

# 1 INTRODUCTION

This review is written in response to a request from the Division of Dermatology and Dental Products (DDDP) for assessment of the container labels, carton and insert labeling for (b) (4) (Spinosad) (b) (4) 0.9% (NDA 22-408).

# 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container label and carton labeling submitted by the Applicant on January 21, 2009. Additionally, the revised insert labeling (submitted on May 1, 2009) was reviewed.

- Container Label (submitted January 21, 2009)
- Carton Labeling (submitted January 21, 2009)
- Insert Labeling (submitted May 1, 2009)
- Product container (bottle and bottle cap)

# 3 RECOMMENDATIONS

Our evaluation of the labels and labeling noted areas where information on the container label, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. 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, please contact OSE Regulatory Project Manager Janet Anderson, at 301-796-0675.

## 3.1 COMMENTS TO THE DIVISION

### 3.1.1 General Comments

DMEPA notes that ONDQA found the proposed dosage form (b) (4)", for this product unacceptable and recommended "suspension" as the proper dosage form. Thus, the dosage form should be changed in all labels and labeling to reflect "suspension" (b) (4)

We note the container label and carton labeling submitted on January 21, 2009 (b) (4) The product strength has since been changed to 0.9% which is reflected in the revised insert labeling submitted on May 1, 2009. However, the Applicant has not submitted a revised container label and carton labeling with the 0.9% strength presentation.

The Applicant provided a working sample of the proposed product container (bottle and bottle cap), see Appendix C. The product is packaged in a white bottle with a white, child-resistant, snap top cap closure and spout that we believe is a satisfactory design for helping to minimize the potential for accidental oral ingestion of the product.

### 3.1.2 Insert Labeling

In the Patient Counseling/Information section, subsection "How to Prevent Reinfestation", there is no information about washing personal items such as bed linens, clothing, combs, brushes, or vacuuming rooms to help prevent the spead of lice and reinfestation. This additional information is important for healthcare practitioners and patients to know, thus, we recommend it be included in this section of the insert labeling.

### 3.2 COMMENTS TO THE APPLICANT

## A. Container Label and Carton Labeling

1. The strength precedes the established name and is positioned inside the brackets [i.e., (b) (4) spinosad)]. The strength should follow the dosage form and be increased in size so that it is easily located on the label. See the recommended presentation below and revise accordingly, using the new strength designation of 0.9%:

| |
|---|
| Proprietary Name<br>(Established Name) Dosage Form<br>Strength |

2. The established name appears to be less than ½ the size of the proprietary name. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features as per 21 CFR 201.10(g)(2).
3. The "Usual Dosage" statement is positioned below the "Directions For Use" statement and has less prominence which makes it difficult to find on the container label and carton labeling and may be overlooked. Relocate the usual dosage statement so that it is positioned above the "Directions For Use" statement.
4. The directions for use state to "Shake (b) (4) bottle well just before use". This statement lacks prominence. Increase the prominence of this statement since it is important for patients to know in order to properly use the product.
5. The route of administration (i.e., "For topical use only") is not on the principal display panel. Ensure the route of administration statement is displayed prominently on the principal display panel and positioned below the product identifying information (i.e., proprietary name, established name, dosage form and strength). Relocating this statement will minimize oral ingestions.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22408 | ORIG-1 | PARAPRO PHARMACEUTICALS LLC | SPINOSAD |

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/s/

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LORETTA HOLMES
11/05/2009

KRISTINA C ARNWINE
11/06/2009

DENISE P TOYER
11/06/2009

CAROL A HOLQUIST
11/06/2009

# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 23, 2009

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Catherine Carr
Regulatory Project Manager
Division of Dermatology and Dental Products

Subject: QT-IRT Consult to NDA 22-408

This memo responds to your consult to us dated June 1, 2009 regarding a TQT study waiver request for (b) (4) (spinosad), a topical product for the treatment of head lice infestations. The QT-IRT received and reviewed the following materials:

- Your consult
- NDA 22-408, Section 2.7.2 Summary of Clinical Pharmacology Studies
- NDA 22-408, Section 2.7.4 Clinical Summary

DDDP has asked for our response to the following question:

Does cardiology agree that spinosad (b) (4) does not need electrocardigraphic evaluation such as a thorough QT/QTc study? It should be noted that the lack of evidence of systemic exposure in humans does not prove that the product is not absorbed in humans. However, for spinosad (b) (4) systemic exposure appears not to be detectable down to low levels, (< 3 ng/mL), the product is to be applied for a short period of time (10 minutes), and the treatment course is limited (one or two treatments per episode of head lice).

**QT-IRT Response:** If you concur with the sponsor's assertion that there is no systemic exposure to spinosad and its metabolites at the clinically relevant doses, a TQT study is not needed for this product. According to the ICH E14 guideline, recommendations for a TQT study apply to new drugs having systemic bioavailability (see section I.B of ICH E14 guideline).

## BACKGROUND

(b) (4), whose active pharmaceutical ingredient is spinosad, is being developed for the control of human head lice (b) (4) in patients (b) (4). (b) (4) contains spinosad at a concentration of (b) (4) and must be left on the scalp for 10 minutes.

Nonclinical Safety Pharmacology

According to the review division, no nonclinical cardiovascular safety pharmacology studies were submitted. ECG evaluation was not performed in the toxicology studies in dogs. An HERG assay was not conducted.

Clinical Pharmacology Experience

The Clinical Program for the development of (b) (4) included three Phase 1 studies that evaluated pharmacokinetics. Spinosad 1% to 2% were evaluated in these PK studies. In all studies 100% of the PK samples collected were below the quantification (<3 ng/mL) for spinosad and/or its metabolites.

*Reviewer's Comment: We did not review the adequacy of the PK data and analytical assay to determine if the sponsor's claim of no systemic exposure is accurate as this type of review is outside the scope of the QT-IRT.*

Clinical Experience

*Source: Summary of Clinical Safety eCTD 2.7.4*

"There were no deaths reported in any of the 11 studies conducted as part of the development plan for (b) (4).

"Across the 11 studies conducted in the development of (b) (4), 6 serious AEs were reported. Of these events, only one (application site erythema) was considered related to treatment (NIX). None of the serious AEs were related to treatment with (b) (4).

"Vital sign measurements and physical examinations were conducted in studies SPN-101-04, SPN-102-05, SPN-103-05, and SPN-106-06; electrocardiograms (ECGs) also were obtained in studies SPN-101-04 and SPN-102-05. There were no vital sign measurements, ECG evaluations, or physical examinations conducted in either study SPN-107-07 or SPN-108-08.

"ECGs were performed on all subjects at entry and exit in study SPN-101-04 and only at entry in study SPN-102-05. In study SPN-101-04, while one subject had an abnormal ECG at entry, all subjects had normal ECGs at the exit visit. In SPN-102-05, no clinically significant abnormalities were reported."

*Reviewer's Comments: There are no reports of cardiac AEs or AEs related to WQT prolongation. While one subject had an abnormal ECG on study entry in SPN-101-04, the sponsor reports that all subjects had normal ECGs in the exit visit.*

## SPONSOR'S PROPOSAL

Based on Guidance Document E14, the clinical evaluation of QT/QTc interval prolongation does not apply to (b) (4), since it is applied topically to the scalp for 10 minutes, and animal and human pharmacokinetic studies show no evidence of absorption or systemic exposure of spinosad.

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/s/
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Christine Garnett
6/23/2009 09:09:14 AM
BIOPHARMACEUTICS

Suchitra Balakrishnan
6/23/2009 10:10:44 AM
MEDICAL OFFICER

Norman Stockbridge
6/23/2009 03:41:56 PM
MEDICAL OFFICER

# DSI CONSULT: Request for Clinical Inspections

**Date:** April 27, 2009

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46

**Through:** Patricia Brown/Medical Officer/Consulting Review Division/HFD-540
Jill Lindstrom/Medical Team Leader for Dermatology/HFD-540

**From:** Catherine Carr, Regulatory Health Project Manager/Division/HFD-540

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

## I. General Information

Application#: NDA 22-408
Sponsor/Sponsor contact information:

ParaPRO Pharmaceuticals, LLC.
ATTN: Reed Tarwater, Ph.D., RAC (Consultant)
Anson Group, LLC
11460 N. Meridan Street, Suite 150
Carmel, IN 46031
Phone: 317-569-9500 X109
FAX: 317-569-9520
rtarwater@ansongroup.com

Drug: TRADENAME (spinosad) (b) (4)
NME: Yes
Standard or Priority: Standard
Study Population < 18 years of age: Yes
Pediatric exclusivity: To be determined

PDUFA: November 22, 2009
Action Goal Date: November 22, 2009
Inspection Summary Goal Date: September 22, 2009

## II. Background Information

This is a new molecular entity NDA for Tradename (spinosad) (b) (4) The proposed indication is for the treatment of head lice *(Pediculus humanus capitis)* infestations (pediculosis capitis) (b) (4)

Pediculosis capitis or head lice is defined as the presence, seen especially in children, of lice on the scalp (b) (4) Each year in the United States (US), millions of adults and children are affected with human head lice.

Two identical Phase 3 pivotal studies were conducted for safety and efficacy. Study Protocol SPN-301-07 (from hereon, Study 301), and SPN-302-07 (Study 302) were multi-center, evaluator/investigator-blind, randomized, three-arm, active-controlled studies. The three arms included the sponsor's product with combing, the sponsor's product without combing, and NIX®. The sponsor's product was compared to NIX®, an active-control, with the objective of establishing superiority of the sponsor's product over NIX®. Treatment consisted of one or two (if lice is not killed at Day 7) 10-minute application of the topical product to the scalp.

For both studies, the primary efficacy endpoint was the proportion of primary subjects that were lice free 14 days after the last application of the drug product (i.e., Day 14 for those subjects with one application, and Day 21 for those with two applications). The secondary endpoint was the proportion of subjects (primary and non-primary subjects) within each treatment group requiring two treatments.

## III. Protocol/Site Identification

| Site # (Name,Address, Phone number, email, fax#) | Protocol # | Number of Subjects | Indication |
|---|---|---|---|
| **Site 03**<br>Robert S. Haber, M.D.<br>Haber Dermatology<br>14077 Cedar Rd, Suite 200<br>South Euclid, OH. 44118<br>(216) 932-5200 | SPN-301-07 | 19 | Head Lice |
| **Site 07**<br>Mark L. Moore, M.D.<br>Concentrics Center for Research<br>9325 Delegates Row<br>Indianapolis, IN. 46240<br>(317)706-3222 | SPN-302-07 | 32 | Head Lice |
| **Site 05**<br>Dow B. Stough, M.D., C.C.T.I.<br>Burke Pharmaceutical Research<br>3633 Central Ave., Suite I<br>Hot Springs, AK. 71913<br>(501)620-4449 | SPN-301-07 | 54 | Head Lice |
| **Site 09**<br>Katie Shepherd, B.A., P.A.<br>Lice Solutions Research Network<br>6758 N. Military Trail, Suite 110<br>West Palm Beach, FL. 33407<br>(561)84209969 | SPN-302-07 | 54 | Head Lice |

## IV. Site Selection/Rationale

Site 03 (Study 301), was selected by having the largest treatment effect – 100% success rate for the sponsor's product without nit combing arm compared to a very low success rate (12.5%) for the NIX® arm. Site 07 (Study 302) was selected for a similar reason (100% with nit combing compared to a 21.4% success rate of NIX®), and also because the success rates for both the sponsor's product arms (with combing and without combing) had 100% treatment success.

Site 05 (Study 301), was selected by having the largest enrollment (52 subjects) and also because the sponsor's product arm with nit combing arm had a lower response rate compared to that of the without nit combing arm. Typically, a higher success rate is expected with nit combing; therefore, it is unusual that the success rate was higher without nit combing.

Site 09 (Study 302) was selected by having the largest enrollment (52 subjects) with large treatment effects.

From the clinical viewpoint, it is also desirable to have representation from different areas of the country due to geographic variations in louse resistance to known treatments.

No specific safety concerns based on adverse events has been identified.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
__X__ High treatment responders (specify): Site 03 (Study 301), 07 (Study 302), 09 (Study 302) had large treatment effect
____ 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.
__X__ Other (specify): Unexpected response at Site 05 (Study 301)

## V. Tables of Specific Data to be Verified (if applicable)

None

Should you require any additional information, please contact Catherine Carr (RPM) at 301-796-2311 or Patricia Brown (Medical Officer) at 301-796-0857.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Director, Division Director (foreign inspection requests only)

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/s/

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Catherine Carr

4/27/2009 09:37:50 AM

**Division of Dermatology and Dental Products**

# REGULATORY PROJECT MANAGER REVIEW (PHYSICIAN LABELING RULE)

**Application Number:** NDA 22-408

**Name of Drug:** TRADENAME (spinosad) (b) (4)

**Applicant:** ParaPRO Pharmaceuticals

**Material Reviewed:**

**Submission Date:** January 21, 2009

**Receipt Date:** January 22, 2009

**PDUFA Due Date:** November 22, 2009

**Submission Date of Structured Product Labeling (SPL):** January 21, 2009

**Type of Labeling Reviewed:** PLR Labeling

## Background and Summary

NDA 22-408, Tradename (spinosad) (b) (4) submitted January 21, 2009 is indicated for the treatment of head lice *(pediculosis capitis)* infestations (b) (4) This is a new molecular entity NDA.

## Review

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant in the 74-day letter. These comments are based on 21 CFR 201.56 and 21 CFR 201.57.

The following issues/deficiencies have been identified in the proposed labeling:

**Highlights Section:**

1. The Initial U.S. Approval statement should be placed immediately beneath the established name of the product.

2. The section "Use in Specific Populations" is listed in the Full Prescribing Information section, but is not listed in the Highlights section. This section with

its sub-sections should be included in the Highlights section for consistency per 21 CFR 201.57(a)(13).

3. The revision dated should appear in bold type.

**Contents (Table of Contents) Section:**

1. The heading "FULL PRESCRIBING INFORMATION: CONTENTS" should appear in all upper case letters and bold type.

2. The table of contents subsection headings should be in regular text, not all upper case text.

**Full Prescribing Information (FPI) Section:**

1. The heading "FULL PRESCRIBING INFORMATION" should appear in bold type.

2. Section 12 "CLINICAL PHARMACOLOGY" is not included in the label. Please provide an updated label with this section per 21 CFR 201.57 (c)(13).

3. Section 13 "NONCLINICAL TOXICOLOGY" is not included in the label. Please provide an updated label with this section per 21 CFR 201.57 (c)(14).

4. In Section 17 "PATIENT COUNSELING INFORMATION", subheadings and identifying numbers should be in bold type to prominently distinguish the subheadings from other labeling information.

5. According to 21 CFR 201.1, manufacturing information should be located at the end of the label, after the Patient Counseling Information section. The manufacturing information should be included for this product according to regulations.

## Conclusion and Recommendation

The labeling deficiencies/issues identified above should be addressed by the applicant. A revised label should be submitted by May 1, 2009.

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/s/
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Catherine Carr
3/31/2009 01:49:57 PM
CSO

Barbara Gould
3/31/2009 02:27:38 PM
CSO

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 22-408 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: (b) (4)
Established Name: Spinosad
Strength: (b) (4)

Applicant: ParaPRO Pharmaceuticals, LLC.
Agent for Applicant (if applicable): Anson Group

Date of Application: January 21, 2009
Date of Receipt: January 22, 2009
Date clock started after UN: N/A
Date of Filing Meeting: February 27, 2009
Filing Date: March 23, 2009
Action Goal Date (optional): TBD User Fee Goal Date: November 22, 2009

Indication(s) requested: Treatment of human head lice and nits

Type of Original NDA: (b)(1) ☑ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

***NOTE:***
*(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A.*

Review Classification: S ☑ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☑ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☑

***NOTE:*** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☑

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☑

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  **N/A** ☑ YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☑

- If yes, has OC/DMPQ been notified of the submission? **N/A** ☑ YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☐ NO ☑
  If no, explain: There is no comprehensive index for the entire submission. However, there are table of contents for individual modules to navigate the submission.

- Was form 356h included with an authorized signature? YES ☑ NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES ☐ NO ☑
  If no, explain: **No index per 21 CFR 314.50(b)**

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES
   This application is: All electronic ☑ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☑
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) **N/A** ☑ YES ☐ NO ☐

   **If an eNDA, all forms and certifications must be in paper and require a signature.**

   If combined paper + eNDA, which parts of the application were submitted in electronic format? **N/A**

   Additional comments:

3. This application is an eCTD NDA. YES ☑
   **If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☑ NO ☐

- Exclusivity requested? YES, _____ Years NO ☑
  ***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☑
  **If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

  ***Note: The correctly worded debarment certification was requested via phone. It will be requested in the 74-day letter.***

  ***NOTE:*** *Debarment Certification should use wording in FD&C Act 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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☑

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? **N/A** ☑ YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☑

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☐ NO ☑
  **(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**
  ***Note: Correspondence signed by Agent. Corrected Form 3454 and/or 3455 signed by applicant was requested via phone. It will be requested in the 74-day letter.***

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☑ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☑ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. **N/A** ☑

- List referenced IND numbers: 66,657

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☑ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) October 31, 2006 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) November 4, 2008 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) July 31, 2007 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

## Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☑ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☑ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: **N/A** ☑

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☑

***Labeling will be provided after mid-cycle per DDMAC.***

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☑ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☑ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☑ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☑ YES ☐ NO ☐

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? **N/A** ☑ YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐ **N/A** ☑

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A** ☑ YES ☐ NO ☐

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☑ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☑ NO ☐
- If a parenteral product, consulted to Microbiology Team? **N/A** ☑ YES ☐ NO ☐

ATTACHMENT

## MEMO OF FILING MEETING

DATE: February 27, 2009

NDA #: 22-408

DRUG NAMES: TRADENAME (spinosad) (b) (4)

APPLICANT: ParaPRO Pharmaceuticals, Inc.

BACKGROUND: NDA 22-408, Tradename (spinosad) (b) (4) is indicated for the treatment of head lice *(pediculosis capitis)* infestations (b) (4). The proposed drug substance, spinosad, is a new molecular entity and a fermentation product.

ATTENDEES:

Susan J. Walker, M.D., Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Patricia Brown, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Team Leader, DDDP
Jerry Wang, Ph.D., Pharmacology Reviewer, DDDP
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
Catherine Carr, M.S., Regulatory Health Project Manager, DDDP
Mohamed Al-Osh, Ph.D., Biostatistics Team Leader, DB III
Carin Kim, Ph.D., Biostatistics Reviewer, DB III
Dennis Bashaw, Pharm.D., Director, DCP III
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPMA II, Branch III
Zhengfang Ge, Product Quality Reviewer, DPMA II, Branch III
Roy Blay, Director of Regulatory, Good Clinical Practices Branch I

ASSIGNED REVIEWERS:

| **Discipline/Organization** | **Reviewer** |
|---|---|
| Medical: | Patricia Brown |
| Secondary Medical: | Jill Lindstrom |
| Statistical: | Carin Kim |
| Pharmacology: | Jianyong (Jerry) Wang |
| Chemistry: | Zhengfang Ge |
| Environmental Assessment (if needed): | TBD |
| Biopharmaceutical: | Dennis Bashaw |
| DSI: | Roy Blay |
| OPS: | TBD |
| Regulatory Project Management: | Catherine Carr |

Per reviewers, are all parts in English or English translation? YES ☑ NO ☐
If no, explain:

CLINICAL FILE ☑ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☑ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known ☐ _____ NO ☑

- 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?
  N/A ☑ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☑ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☑ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☑ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☑
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☑ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☑ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☑ NO ☐
- Sterile product? YES ☐ NO ☑
  If yes, was microbiology consulted for validation of sterilization?
  N/A YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ The application is unsuitable for filing. Explain why:

☑ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☑ Filing issues to be communicated by Day 74.

**ACTION ITEMS:**

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

3. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Catherine Carr, MSc.
Regulatory Health Project Manager

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/s/
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Catherine Carr
3/31/2009 01:55:04 PM
CSO

Barbara Gould
3/31/2009 02:23:30 PM
CSO