CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review

Date	November 8, 2010
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA #	22-408
Applicant	ParaPRO Pharmaceuticals, LLC
Date of Submission	July 26, 2010
PDUFA Goal Date	January 26, 2010
Proprietary Name	TRADENAME
Established (USAN) names	Spinosad
Dosage forms / Strength	Suspension/0.9%
Proposed Indication(s)	Topical treatment of head lice infestation (b) (4)
Recommended:	*Approval*

1. Introduction

TRADENAME (spinosad) suspension, 0.9%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of head lice infestation in patients (b) (4). The active ingredient, spinosad, is a new molecular entity which is not marketed as a drug in the United States.

The initial application, submitted on January 21, 2009, received an Approvable action letter dated November 18, 2009. The applicant submitted a Complete Response on July 23, 2010, and this brief Team Leader Review Addendum will discuss the Complete Response. The reader is referred to Cross-Discipline Team Leader Review and Cross-Discipline Team Leader Review Addendum by Jill Lindstrom, MD dated November 2, 2009 and November 5, 2009 retrospectively, for discussion of the original application.

2. Background

The following issues were articulated in the **Complete Response** letter (November 18, 2009):

1. "FDA agrees that spinosad, containing spinosyns A and D in a ratio of approximately 5:1, is a single active ingredient. However, we have recently approved a product containing benzyl alcohol (present at 5%) as an active ingredient for the treatment of head lice. This would indicate that your product contains two active ingredients: spinosad and benzyl alcohol (b) (4)
    - A. Provide information to support approval of your product according to the regulations for fixed-combination prescription drugs at 21 CFR 300.50.
    - B. Provide pharmacokinetic data for benzyl alcohol in lice-infested subjects.
    - C. Submit complete CMC information on the drug substance, benzyl alcohol.
    - D. Submit complete nonclinical information to support the safety of benzyl alcohol per the ICH M3 (R2) guidance titled "Guidance on Non-Clinical

Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

2. Although your maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of TRADENAME (spinosad) Suspension, 0.9%, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to greater surface-to-volume ratio and the effects of the infestation itself on the scalp.

(b) (4)

3. Sufficient information has not been submitted to assure the identity, strength, purity, and quality of the spinosad drug substance and the drug product.

Drug Substance:

A. In addition to a cross reference to DMF 17795, submit a regulatory specification for acceptance of spinosad to the NDA

Drug Product:

B. Include ID tests in the excipient specifications for Ceteareth-20 and Stearalkonium Chloride

C. Submit an updated drug product specification which reflects the revised definition for "active ingredient." The specification should also reflect the revised definitions for "Related Substances," "Impurities," and the Acceptance limit, based on clarifications you provided in the teleconference held on August 28, 2009

D. Based on the retention time table for the HPLC method used, placebo (b) (4) and spinosyn D ((b) (4) very closely. Provide data to demonstrate that the assay value for spinosad D is not compromised by the placebo peak.

E. Provide more detailed information regarding (b) (4) the drug product when stored under accelerated stability conditions.

F. (b) (4) was observed in the drug product samples provided in May 2009. Provide the following information to address the effects of (b) (4) on drug product quality.

1. Data indicating when (b) (4) starts during storage and whether the storage conditions have any effect (b) (4)
2. Data to demonstrate that content uniformity (b) (4) drug product is re-established after shaking;
3. A description of the physical form of the drug product (e.g. lotion-like, solution-like, etc.) in the Appearance specification for the drug product. This description is needed, in addition to color as proposed, in the Acceptance criteria for the Appearance test.

A Post-Action Meeting was convened on March 25, 2010. The Agency requested further clarification regarding whether the presence of benzyl alcohol in the ParaPRO product is a formulation necessity, and the scientific data upon which the assertion that benzyl alcohol be considered an inactive ingredient is based.

The applicant provided responses with a submission dated April 13, 2010 and has included those responses in the resubmission, including support for the sponsor's position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation.

3. CMC/Device

Several deficiencies involving the drug product were identified during the review of the initial application. The Complete Response letter advised the applicant that sufficient information has not been submitted to assure the identity, strength, purity, and quality of the spinosad drug substance and the drug product (item# 3A-F; Complete Response letter dated November 18, 2009).

In the current submission the applicant has provided information in response to each of the requests detailed above. The applicant concludes that the benzyl alcohol is a formulation necessity (b) (4) and safety profile. The applicant also stated that "intent of having benzyl alcohol in the spinosad product formulation (b) (4) as the alcohol of choice with minimal interference to hair and scalp quality". The formulation evaluated consists primarily of (b) (4) isopropyl alcohol, (b) (4) benzyl alcohol, (b) (4) hexylene glycol, (b) (4) propylene glycol and (b) (4) water. Spinosad solubility in water is very limited. The non-aqueous formulation components provide the solvating properties, (b) (4) The applicant evaluated criteria for the suitability of each (b) (4) in the spinosad formulation include: solubility, compendial status, safety, history of use, (b) (4). Based on information provided in this submission, it appears that the applicant made a reasonable argument for benzyl alcohol as a legitimate component of the formulation.
The reader is referred to the review of Dr Patricia Brown for a full discussion.

The information regarding item # 3 A-F has been reviewed by the chemistry reviewer with the following conclusion:

- The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure the strength, purity, and quality of the drug product during the 36-month of expiration dating period.

- All labels and labeling have adequate information as required.

- All facilities have "Acceptable" site recommendations from the Office of Compliance.

The CMC reviewer, Zhengfang Ge, Ph.D., recommended *Approval* from the CMC perspective. No CMC postmarketing studies are recommended for this drug product. For a full discussion, the reader is referred to the reviews of Patricia Brown, MD, dated December 9, 2010, and Zhengfang Ge, PhD dated September 28, 2010.

4. Nonclinical Pharmacology/Toxicology

The sponsor did not provide any new nonclinical information in this resubmission.
(See Pharmacology/Toxicology Review of the original application by Jianyong Wang, Ph.D. dated September 3, 2009)

The Pharmacology/Toxicology Reviewer, Jianyong Wang, Ph.D., recommended *Approval* from the pharmacological/toxicological perspective. No nonclinical postmarketing studies are recommended for this drug product.
(See Pharmacology/Toxicology Review dated September 30, 2010)

5. Clinical Pharmacology/Biopharmaceutics

Two issues presented in the Complete Response letter (dated November 18, 2009) dealt with the pharmacokinetics of benzyl alcohol (item# 1B) and dermal absorption in pediatric patients (item# 2): The sponsor has not provided information to demonstrate the PK profile of benzyl alcohol, as in their opinion, there is no issue to respond to as they maintain benzyl alcohol is not an active ingredient, therefore, no need for additional or "any" pk data related to benzyl alcohol. However, there is safety concerns related to benzyl alcohol, specifically that there is an increased risk of systemic absorption in children less than six months of age (because of the high ratio of skin surface are to body mass and the potential for an immature skin barrier), and there is an increased risk for gasping syndrome in premature infants. No data on the pharmacokinetics of benzyl alcohol in subjects with or without active lice infestation were provided. Therefore, for the reasons stated above, this information is needed. The applicant could conduct a single trial to obtain pharmacokinetic data for both benzyl alcohol and spinosad in subjects 6 months to 4 years of age with active lice infestation.

(b) (4)

There is a lack of *in vivo* "pk data in subjects with active lice infestation below the age of 4years. For topically applied products, bioavailability testing should be accomplished in subjects with the disease of interest as normal skin is a poor surrogate for diseased skin
The reader is referred to the review (dated October 6, 2010) by Dr. Edward D Bashaw, Pharm.D, who now recommends *Approval* from a clinical pharmacology perspective.

6. Clinical/Statistical- Efficacy

TRADENAME suspension was demonstrated to be statistically superior to an active comparator in each of two well-controlled pivotal, Phase 3 trials.

The applicant submitted data from two pivotal trials (Study SPN-301-07 and Study SPN-302-07) to establish the effectiveness of their product in the treatment of head lice infestation. These trials were multi-center, prospective, randomized, double-blind, parallel group studies with three arms, TRADENAME suspension without combing, TRADENAME suspension with combing, and active control [NIX (Permethrin 1%)]. In these trials TRADENAME suspension was applied for 10 minutes and repeated in one week (7 days) if live lice were noted at that time. Efficacy was assessed 14 days after the last treatment, and success was defined as the absence of live lice.
The primary efficacy endpoint is the proportion of subjects with treatment success at 14 days after the last treatment (see Table 1):

	TREADNAME (spinosad) suspension, 0.9%	**TREADNAME (spinosad) suspension, 0.9%**	**NIX**	
	With nit combing	Without nit combing		**P-value**
SPN-301-07	N=23 19 (82.6%)	N=91 77 (84.6%)	N=89 40 (44.9%)	< 0.001
SPN-302-07	N=21 17 (81.0%)	N=83 72 (86.7%)	N=84 36 (42.9%)	< 0.001

Table 1: Source: Clinical review NDA 22-408, Dr Patricia Brown, MD 2009

The majority of the subjects in the TRADENAME suspension arms required only one treatment.
The reader is referred to Cross-Discipline Team Leader Review by Jill Lindstrom, MD dated November 2, 2009 for discussion of the original application.

In summary, the applicant has established the efficacy of their product in the treatment of head lice infestation. The rider is referred to the reviews of Patricia Brown, MD and Lisa Kammerman, PhD for a complete discussion of the efficacy results.

7. Safety

During the development of TRADENAME suspension 1,561 subjects were evaluated, 1,040 of whom were exposed to TRADENAME suspension. Of these, 560 subjects were exposed to the final to-be-marketed product, TRADENAME suspension, 0.9%, in a dose that reflected anticipated labeled use (552 subjects with lice infestation in the Phase 3 trials and 8 healthy subjects in the infant PK study). In the pivotal trials, pediatric exposure in the 4 years and younger age group appears adequate (85 subjects); however, only 20 subjects were in the youngest group age (6-24 months).
In the pivotal trials, 400 subjects received one application and 152 subjects received two applications (treatment duration of 10 minutes per application).

There were no deaths or serious adverse events (SAEs) attributable to TRADNAME suspension. The most frequently reported adverse event (AE) was application site erythema (3.1% TRADENAME suspension; 6.8% NIX). Ocular hyperemia was the second most common AE (2.2% TRADENAME suspension; 3.3% NIX), followed by application site irritation (0.9% TRADENAME suspension; 1.5% NIX).

The reader is referred to the Clinical Review (dated March 20, 2009) by Patricia Brown, MD, for full discussion of the safety results.

8. Pediatrics

The applicant conducted Phase 3 trials in subjects 6 months of age and older, the relevant population for head lice infestation (b) (4)
The applicant requested a pediatric waiver for children less than six months of age based on the rationale that studies are "are highly impracticable since the number of subjects in this age group is very small." Although, that studies would be impracticable because the number of patients aged less that 6 months is low, it is recommended that studies in children 6 months of age and younger be waived because of safety concerns related to benzyl alcohol, specifically that there is an increased risk of systemic absorption in children less than 6 months of age because of the high ratio of skin surface to body mass and the potential for an immature skin barrier, and there is an increased risk for gasping syndrome in premature infants. This will be addressed in labeling.

Benzyl alcohol is an excipient in the nonprescription products [e.g. ACT Children's fluoride rinse (for children 6 years and older), Aveeno Baby sunscreen (for children 6 months and older), Aveeno Daily Baby Moisturizing Lotion, Aveeno Baby Lotion Calming Comfort, Rite Aid Gentle Baby Lotiuon, Johnson & Johnson Baby Lotion). Of 1,649 products currently on the market that contain benzyl alcohol, 39 are marketed for infants according to the Cosmetic Safety Database (2008). It is likely that the above baby products contain lower concentrations of benzyl alcohol than TRADENAME (spinosad) Suspension. However, these baby products may be applied over most of the skin surface area, may be applied repeatedly over the course of the day, may not be rinsed off between application, and are frequently covered by diapers or clothing resulting in an occluded application site. In contrast, TRADENAME (spinosad) Suspension is applied to a small area of the body (the hair and scalp), left on for only 10 minutes and is then rinsed off. Therefore, although the systemic bioavailability of benzyl alcohol from TRADENAME (spinosad) Suspension, 0.9% is unknown, the common use on infants of topical cosmetic products containing benzyl alcohol suggests that absorption of benzyl alcohol from this drug product during its brief contact with the scalp is unlikely to represent a risk to the intended patient population.

(b) (4) the applicant will need to conduct a maximal usage pharmacokinetic/safety trial in children with active head lice infestation aged 6 months to 4 years. In addition to pharmacokinetic data for spinosed, the applicant will need to provide pharmacokinetic data for benzyl alcohol as well (for the reason stated above).

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}. Safety assessment should include: a. systemic safety (vital signs, laboratory evaluation), b. local safety (scalp/ocular evaluation; query for pruritus), and c. adverse events.
The application was presented to the Pediatric Review Committee (PeRC) on September 22, 2010. The committee concurred with the Division's recommendation to grant a waiver for pediatric patients aged 0 to 6 months, and a deferral for pediatric patients aged 6 months to 4 years. The committee agreed with the plan to conduct PK/PD study in 24 children with active lice infestation 6 months through 4 years of age [Group 1: 6 months to <1 year (12subjects); Group 2: 1 year to 4 years (12 subjects). The committee commented that the Division may consider obtaining safety information as well.

The committee agreed that the Pediatric Assessment provided by the applicant for ages 4 years and older is satisfactory.

Safety information in labeling regarding benzyl alcohol may need to be revised pending results from the maximal usage pharmacokinetic/safety trial in children with active head lice infestation aged 6 months to 4 years.

9. Labeling

The proprietary name has not been established. The product is referred to as TRADENAME (spinosad) Suspension, 0.9%, in this review.

In the current submission, the applicant resubmitted a request for proprietary name review by the FDA. The applicant requests that the FDA evaluate the name "Natroba" as the primary proprietary name for use for the spinosad drug product. (b) (4)

The Division of Drug Marketing, Advertising, and Communication (DDMAC) does not have any promotional issues with the name "Natroba." (b) (4)

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The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.
Significant changes incorporated into revised draft labeling, following labeling review, include:

- 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
  (See Pediatric and Maternal Health Staff Review dated November 6, 2010 by Jenine A Best)

Labeling negotiations have not concluded at the time of this review.

10. Recommendations/Risk Benefit Assessment

Recommended regulatory action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 22-408, TRADENAME (spinosad) suspension, 0.9% pending agreement of the applicant with the recommended labeling revisions.

Risk Benefit Assessment:

- The risk-benefit ratio supports approval of this product for the treatment of head lice infestation in patient 4 years of age and older.

Recommendation for Postmarketing Risk Management Activities:

- Postmarketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed.

Recommendation for Postmarketing Requirements:

- To fulfill the requirements of PREA, the applicant will need to conduct a maximal usage pharmacokinetic/safety trial in children with active head lice infestation aged 6 months to 4 years.

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/s/

GORDANA DIGLISIC
12/09/2010