CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 10th, 2010
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA	22-408
Applicant Name	ParaPRO Pharmaceuticals, LLC
Date of Submission	Original Submission: January 22nd, 2009 Complete Response: July 26th, 2010
PDUFA Goal Date	January 26th, 2011
Proprietary Name / Established (USAN) Name	Tradename/Spinosad
Dosage Forms / Strength	Topical/0.9%
Proposed Indication(s)	Treatment of head lice
Recommended Action for NME:	***Approval***

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Patricia Brown, M.D.
Statistical Review	Carin Kim, Ph.D.
Pharmacology Toxicology Review	Jianyong Wang, Ph.D.
CMC Review/OBP Review	Zhengfang Ge, Ph.D.
Clinical Pharmacology Review	Dennis Bashaw, Pharm.D.
DDMAC	Lynn Panholzer, Pharm.D. Sheetal Patel, Pharm.D.
CDTL Review	Gordana Diglisic, M.D.
OSE/DMEPA	Loretta Holmes, B.S.N., Pharm.D.
OSE/DRISK	Steve Morin, B.S.N.
PMHS Review	Jeanine Best, M.S.N.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
PMHS=Pedatric and Maternal Health Staff
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

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 original submission of January 22nd, 2009 received a Complete Response action. My recommendation is that this application provides adequate information to address the deficiencies cited in the previous action, and the product is ready for approval.

2. Background

Head lice infestations present an ongoing public health concern. While reliable data on how many people become infested with head lice each year in the United States are not available, CDC information indicates that an estimated 6 million to 12 million infestations occur each year in the US among children 3 to 11 yrs of age. Resistance has been reported to many of the available therapies, and the availability of additional treatments will enhance the options available to patients and physicians.

The Agency first cycle review concluded with a Complete Response letter detailing informational needs in three areas: characterization of the drug substance and drug product, bioavailability information, and characterization of the active ingredient. I will briefly summarize these areas below, and provide additional information within the body of this review. The basis for my summary review includes both the sponsor's Complete Response submission and the individual discipline reviews.

Characterization of drug substance and drug product: The first cycle application did not include adequate information to assure the identity, strength, purity and quality of the Spinosad drug substance and drug product. Adequate information has now been submitted and described fully by the CMC reviewer.

Maximal Usage Study: The (b) (4) did not include adequate information regarding systemic bioavailability in children (b) (4) The sponsor has (b) (4) the application to provide for approval in children 4 yrs and older, for whom adequate information has been provided. The sponsor will complete additional studies for the deferred population post approval.

Clarification of the active pharmaceutical ingredient:

The intended drug substance is Spinosad, a novel complex mixture resulting from fermentation by *Saccharopolyspora spinosa*, an acinetobacterium found in soil. Spinosad contains two components, Spinosyn A and D, and is thought to cause neural excitation in insects, leading to death, and is used as an agricultural insecticide. Spinosad is completely solubilized in the drug product, Natroba (Spinosad) suspension 0.9%. The (b) (4) substances include benzyl alcohol, a substance commonly included as an excipient in topical products. During the first cycle review of this application, benzyl alcohol was the subject of another NDA application (22-129) approved for the **first time** as an **active pharmaceutical ingredient** on April 9th, 2009 for the treatment of head lice. As a result of the novel/new designation of benzyl alcohol as an active pharmaceutical ingredient for the treatment of head lice, the sponsor was asked to provide information to support approval of their product with a single active ingredient (Spinosad).

The applicant has provided adequate information to support benzyl alcohol as a formulation necessity in their drug product. Final product formulation of topical drug products is a complex process which balances delivery of the drug substance (i.e. solubility/presentation of API), with product acceptability (odor, texture, cosmesis). The applicant considered many elements in reaching their final formulation, including a variety of solubilizing substances, which are detailed in the CMC section of this review. The applicant developed their formulation with benzyl alcohol (b) (4) Benzyl alcohol is an extremely common excipient in a variety of products applied to hair, including conditioners, shampoos, hair coloring agents and soaps. (b) (4) .

The applicant requested agency advice throughout the development period, including a preIND meeting, End of Phase 2 meeting and a Special Protocol Assessment, and for all these communications received advice consist with developing the product with a single active pharmaceutical ingredient. (b) (4) benzyl alcohol was presented (b) (4) , and the agency did not have reasonable information to compel the sponsor to explore the role of benzyl alcohol as a potential active ingredient. Therefore, for this product, based upon the history of Spinosad formulation development and the advice provided by the agency, benzyl alcohol was accepted as an excipient early in the development program with an acknowledged necessary function in the formulation (b) (4) .

In my opinion, there is no useful safety or efficacy information needed beyond the information already requested and provided by the sponsor. The contribution of the Spinosad component alone has been demonstrated (see clinical studies section) and the safety and efficacy of the drug product has been successfully demonstrated. The product formulation and clinical development program were agreed upon with the agency prior to the approval of benzyl alcohol as an active pharmaceutical ingredient, and the sponsor has adequately completed all requirements as described by the agency. The sponsor has pursued a successful development program and I concur with the clinical reviewer's conclusion that the results of the clinical

studies are robust (see clinical studies section for details). In my opinion the sponsor has provided adequate information to support approval of Spinosad suspension with a single active pharmaceutical ingredient. No additional trials are necessary or appropriate prior to the approval of this product for treatment of children 4 years of age and older.

3. CMC

The drug substance, Spinosad, is a fermentation product of *Saccharopolyspora spinosa*. Spinosad is a complex mixture of spinosyns, which are cationic amphiphilic compounds composed of large ring complexes, tertiary amines and sugars. Spinosyn A and spinosyn D are present at a ratio of 5:1 and comprise (b) (4) of the drug substance by weight; related minor spinosyns comprise an additional (b) (4) of the drug substance weight. Because 1) spinosad is a fermentation product, 2) spinosyn A and D are present in a fixed ratio and both show evidence of activity, and 3) further purification presented significant hardship, the Agency recognized spinosad as a single active ingredient in which spinosyn A and D are the active components and the other spinosyns are related compounds (Agency communication dated May 17, 2007).

The drug product, spinosad suspension, 0.9%, is a viscous peach-colored liquid which contains the active ingredient, spinosad, in a vehicle consisting of water, isopropyl alcohol, benzyl alcohol, hexylene glycol, propylene glycol, etearyl alcohol, stearalkonium chloride, ceteareth-20, hydroxyethyl cellulose, butylated hydroxytoluene, and FD&C Yellow #6.

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(b) (4) of the Spinosad component is important in order to maximize the effectiveness of the drug product, and the benzyl alcohol is a critical component (b) (4) . Both benzyl alcohol and isopropyl alcohol (b) (4), while propylene glycol and hexylene glycol (b) (4) and cetostearyl alcohol and ammonyx-4 (b) (4). Hydroxyethylcellulose (b) (4) . Spinosad (b) (4) in water is limited. The composition is provided in the following table:

Table 1: Spinosad Composition

Ingredient	Percent Formula (%w/w)	Purpose
Benzyl alcohol	(b) (4)	
Butylated hydroxytoluene		
Ceteareth-20		
Cetearyl alcohol		
FD&C Yellow #6		
Hexylene glycol		
Hydroxethyl cellulose		
Isopropyl alcohol		
Propylene glycol		
Spinosad	0.9	Active ingredient
Stearalkonium chloride	(b) (4)	
Water		

Source: adapted from CMC review of NDA 22-408, Zhengfang Ge, PhD, 9/23/2009, p.17.

(b) (4)

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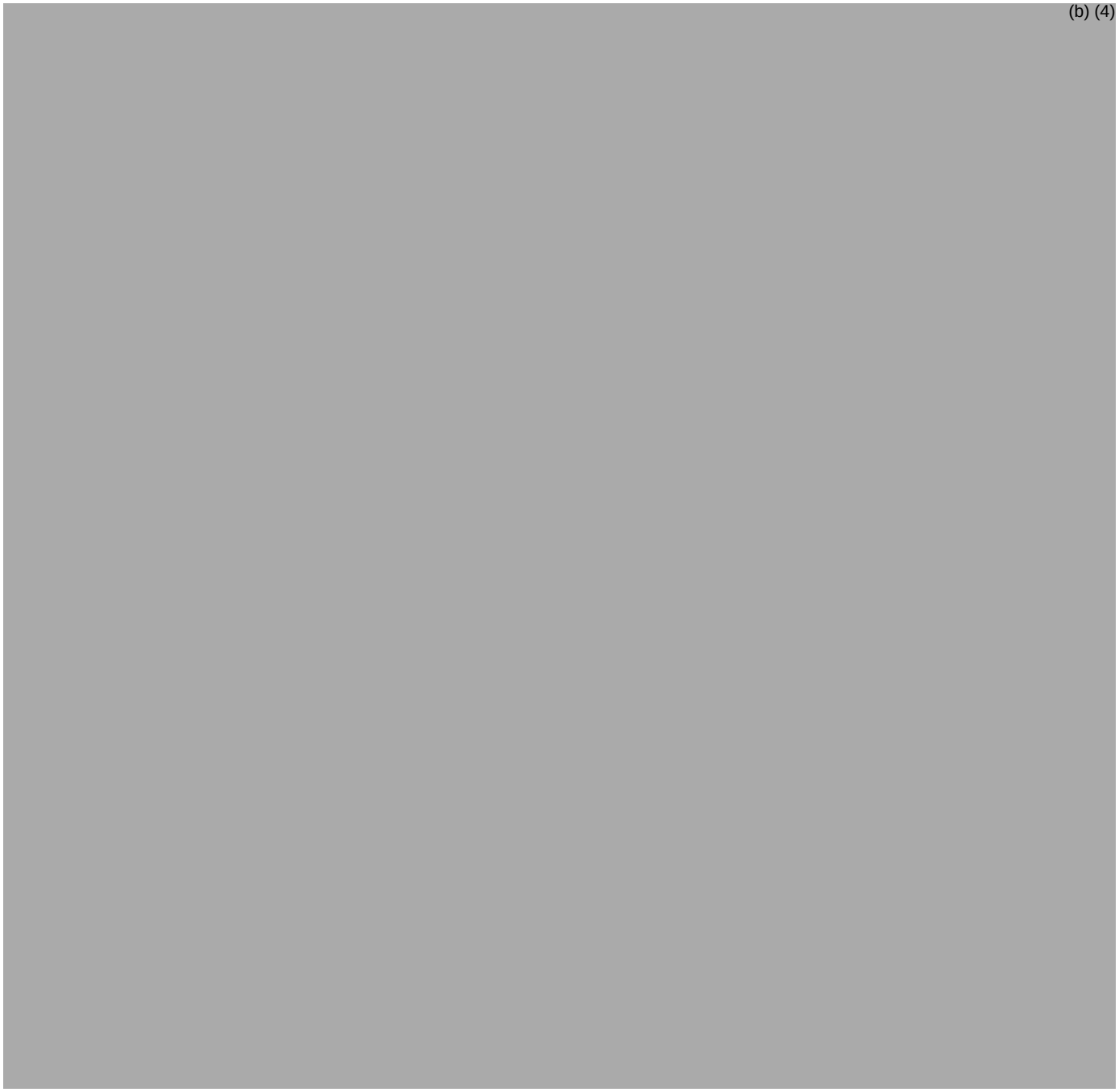
(b) (4)



I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. The CMC reviewer recommends approval.

4. Nonclinical Pharmacology/Toxicology

Repeat dose dermal toxicology studies did not reveal significant dermal or systemic toxicity in rabbits (three weeks) or minipigs (four weeks). Repeat dose oral toxicology studies in rats, mice and dogs identified vacuolation and inflammation in a variety of organs, but did not reveal neurotoxicity. Spinosad was not found to be genotoxic in mutagenicity assays, and carcinogenicity studies were negative in mice and rats. Spinosad 1.8% suspension caused mild reversible irritation in the rabbit eye study, and did not induce a phototoxic reaction in mice irradiated with UVA light. Reproductive toxicity studies in rats and rabbits did not identify a teratogenic signal, and support a pregnancy category designation of Category B.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

In published studies to determine the mode of action of the spinosyns as an insecticide, it was found to directly excite the insect nervous system, initially causing involuntary tremors and muscle contractions by acting on the CNS, leading to death. This excitation is considered to be due to persistent activation of nicotinic acetylcholine receptors and gamma-butyric acid gated ion channels in the insect's neurons, a mechanism similar to nerve gas.

Systemic bioavailability was evaluated in three maximal usage trials using a 1.8% Spinosad product, not the 0.9% product proposed for marketing. As this represents a higher concentration than the to-be-marketed product, and no blood levels were detected in vivo, this is acceptable. All three trials were conducted using a formulation that contained this two-fold higher concentration of the active ingredient than is in the to-be-marketed formulation (1.8% spinosad vs. 0.9% spinosad, respectively). The pharmacokinetic evaluation included assessments of spinosyn A and spinosyn D plasma concentration levels over time and a derivation of parameters that included $AUC_{0\text{-}tmax}$, C_{max}, and T_{max}. Neither nor its metabolites were detectable in plasma samples (Table 5).

Table 5: Spinosad Bioavailability

Study	N	Age range	Disease status	Number of Samples	Spinosad/metabolite concentration
SPN-101-04	23	21-60 years	Healthy non-infested	614/ (100%)	BLQ*
SPN-103-05	14	4-15 years	Infested	136 (100%)	BLQ
SPN-106-06	8	6-23 months	Healthy non-infested	48 (100%)	BLQ

* = Below Limits of Quantification, i.e. <3ng/ml
Source: OCPB review of NDA 22-408, CAPT E. Dennis Bashaw, PharmD; 10.6.2009; Dr. Jill Lindstrom CDTL Review

I concur with the clinical pharmacology and clinical reviewers that while the lack of detectable systemic levels is generally reassuring, the data is inadequate for children younger than 4 years of age due to the paucity of subjects, especially at the lower end of the age range, and the fact that those subjects did not have lice infestation. The stratum corneum, which is a major barrier to absorption of topically-administered drugs, may be disrupted in individuals infested with lice in part due to the local reaction that occurs at the sites at which the louse obtains a blood meal, as well as mechanical disruption caused by scratching. The surface-to-volume ratio will also be greater in the youngest subjects, and systemic exposure is likely to be greatest in this age group.

(b) (4) in the population younger than 4 years, systemic exposure data should be obtained in infested children. I concur with the recommendation to obtain pharmacokinetic data for both benzyl alcohol and spinosad in subjects 6 to 48 months of age in a single study, providing pharmacokinetic data across the affected age range for spinosad, which is a new molecular entity, and pharmacokinetic data in the most relevant age cohort (youngest subjects) for benzyl alcohol. Potential safety concerns regarding benzyl alcohol exposure arise from inadvertent systemic exposure (injection, etc) and are applicable to a very young population of neonates and premature infants, whose immature hepatic development renders them unable to metabolize benzyl alcohol. This product is not intended for systemic use, but it seems reasonable to obtain the benzyl alcohol exposure information (b) (4) in younger children.

I concur with the design of the post-marketing study, an open label study PK study of TRADENAME (spinosad) 0.9% suspension under maximum use conditions in patients with active head lice infestation, aged 6 months to 4 years, with a minimum of 24 evaluable patients. The 24 children should be divided by age into two groups: Group 1 - 12 patients between 6 months and < 2 years; Group 2 - 12 between 2 years and 4 years. Within each of the groups there should be a generally equal distribution of males and females. Patients should otherwise be healthy, except for the 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}. Safety assessment should include: a) systemic

safety (vital signs, lab evaluation) b) local safety (scalp/ocular evaluation; query for pruritus) and c) adverse events. Given the age range studied a mutually agreeable reduced pharmacokinetic sampling program is acceptable.

No QT/QT_c study was obtained. Although Spinosad is a new molecular entity, systemic exposure was below the level of detection. Because of the short application time, absence of detectable systemic exposure, and limited treatment duration, the clinical and clinical pharmacology reviewers recommended that a TQT study was not warranted. Consultation was obtained from the QT-IRT team, who agreed with this assessment.

I concur with the conclusions reached by the clinical pharmacology and clinical reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable to this application.

7. Clinical/Statistical-Efficacy

The applicant submitted data from two pivotal trials, Study SPN-301-07 and Study SPN-302-07, to establish the effectiveness of their product when applied for 10 minutes and repeated if live lice were observed at one week. These trials (301 and 302) 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). Households were enrolled if one or more member 6 months of age or older was infested with at least 3 live lice; the youngest infested household member with at least 3 live lice was the index subject (primary efficacy cohort) and other infested household members (with at least 1 live louse) were enrolled in the secondary cohort. All subjects in a household received the same treatment. Subjects applied the requisite amount of clinical trial material, depending on hair length, for 10 minutes on day 1, and repeated the application on day 7 if live lice were still present at that time. Efficacy was assessed 14 days after the last treatment (day 14 for subjects who received only one treatment, and day 21 for subjects who received 2 treatments), 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, shown in the Table 6.

Table 6: Efficacy Evaluation

	TRADENAME (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

*P-value: TRADENAME (spinosad) suspension, 0.9%, w/out nit combing, vs. NIX
Source: Adapted from clinical review of NDA 22-408, Dr. Patricia Brown, MD; 10.xx.2009, pp 48-9.

In both studies, the spinosad arms demonstrated similar point estimates regardless of combing, and the results are also consistent across the two pivotal trials. In both studies, TRADENAME (spinosad) suspension, 0.9%, used according to proposed labeling, is superior to NIX in the treatment of head lice infestation

In the phase 2 program, the sponsor explored comparisons of various concentrations of Spinosad to vehicle. In addition to providing dose ranging information, these phase 2 studies provide information demonstrating the contribution of the Spinosad component. The chemistry reviewer has confirmed the formulation used in Study 202-06. The spinosad 1.0% arm utilized product from LOT 7107.001, which was the manufacturer's to-be-marketed formulation. The vehicle arm utilized product from LOT 7105.001, the to-be-marketed formulation minus spinosad.

201-05: This was a single center, investigator/evaluator-blind, 4 arm, parallel group vehicle controlled study comparing Spinosad (.5%, 1% and 2%) with the vehicle. Subjects received treatment twice daily, day 0 and 7, and the proportion of subjects with live lice/nits was tabulated pre/post treatment on day 0,7,14. This study allowed nit combing on subjects after each treatment. The spinosad arms demonstrated consistent superiority to vehicle in percentage of lice-free subjects, as demonstrated in Table 7 below.

Table 7: Treatment Success (Lice-Free) Study SPN-201-05: ITT Population

Time point	Vehicle	Spinosad		
	0%	0.5%	1.0%	2.0%
	N=9	N=8	N=9	N=9
Day 0 Pre-Treatment	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 0 Before Combing	3 (33.3%)	6 (75%)	7 (77.8%)	6 (66.7%)
Day 0 After Combing	6 (66.7%)	7 (87.5%)	9 (100%)	8 (88.9%)
Day 7 Pre-treatment	2 (22.2%)	7 (87.5%)	9 (100%)	9 (100%)
Day 7 Before Combing	6 (66.7%)	8 (100%)	9 (100%)	9 (100%)
Day 7 After Combing	8 (88.9%)	8 (100%)	9 (100%)	9 (100%)
Day 14	8 (88.9%)	8 (100%)	9 (100%)	9 (100%)

Source: Sponsor's NDA, Clinical Study Report for Study SPN-201-05, Table 11.4.1-1, p. 36.

201-06: This was a multi-center, investigator-blind, 3 arm, parallel group vehicle controlled study comparing Spinosad (0.5% and 1%) with vehicle. A total of 122 subjects were enrolled. Subjects received one treatment on Day 0, and the proportion of subjects with live lice/viable nits was tabulated on days 7 and 14. Nit combing was not performed. At day 7 the proportion of successes in the Spinosad treatment groups (91.7% and 92%) were similar to one another and greater than the vehicle treatment group (49%). At day 14 the proportion of successes in the Spinosad treatment groups (86% and 82%) was greater significantly than the vehicle treatment group, as illustrated in Table 8 below.

Table 8: Primary Efficacy Outcome: Study SPN-202-06

	Spinosad 0.5%	Spinosad 1.0%	Vehicle 0%	p-value
	N=40	N=36	N=43	
Day 7				
Success	37 (92.50%)	33 (91.67%)	21 (48.84%)	<0.0001[a], <0.0001[b]
Failure	3 (7.50%)	3 (8.33%)	22 (51.16%)	
Day 14				
Success	33 (82.50%)	31 (86.11%)	11 (25.58%)	<0.0001[a], <0.0001[b]
Failure	7 (17.50%)	5 (13.89%)	32 (74.42%)	

[a] P-value from Chi-Squared comparison of the success rate in Spinosad 0.5% to vehicle

[b] P-value from Chi-Squared comparison of the success rate in Spinosad 1.0% to vehicle

Source: Sponsor's NDA, Integrated Summary of Efficacy, Table 6.2.1.2-1, p. 57.

Note: As studied, the 0.5% formulation contained .45% spinosad, the 1.0% contained .9% spinosad, and the 2% contained 1.8% spinosad.

8. Safety

The applicant has adequately demonstrated the safety of this drug product when used to treat head lice infestation (pediculosis capitis) in children 4 years of age and older.

The safety database includes 1,561 subjects of whom 1,040 were exposed to spinosad at various concentrations. 715 subjects were exposed to TRADENAME, including 552 subjects in phase 3 trials.

The most common adverse event reported was application site erythema, occurring in 3.1% of subjects exposed to TRADENAME and in 6.8% of subjects exposed to NIX. During the 11 studies in the clinical development program, no subjects dropped out due to an adverse reaction evaluated as related to spinosad. In the phase 3 trials, no subjects dropped out due to adverse events.

A post-marketing requirement under PREA will be requested to provide systemic exposure information for spinosad and benzyl alcohol in children less than 4 yrs of age with headlice infestation. Benzyl alcohol toxicity from topical exposure has not been demonstrated. **Systemic** benzyl alcohol exposure has been reported to result in gasping syndrome in premature infants and neonates when benzyl alcohol was inadvertently administered systemically. Additional pharmacokinetic information will be requested out of an abundance of caution, as there are no safety concerns raised by this application. During the conduct of the pharmacokinetic trial for spinosad bioavailability in children less than 4 yrs of age, the sponsor has agreed to also evaluate systemic benzyl alcohol exposure.

9. Advisory Committee Meeting

NDA 22-408 was not presented to the Dermatology and Ophthalmology Drugs Advisory Committee. No safety signals were identified during the development program. In addition, neither the indication nor the application presented novel issues which would have warranted advisory committee input.

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10. Pediatrics

The Pediatric Research Equity Act of 2007 (PREA) requires that applicant assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations using age appropriate formulations. The applicant submitted a Request for Waiver of Pediatric Studies under 21 CFR 314.55(c) (3) (i) and this was discussed with Pediatric Review Committee (PeRC).

Waiver: The Pediatric Review Committee agreed with waiver of pediatric studies ages 0 up to 6 months because a) studies are highly impractical or impossible b) the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of patients in these age groups and c) the product would be unsafe in the pediatric age group for which a waiver is requested, based upon the potential toxicity of benzyl alcohol in neonates and premature infants.

Deferral: The PeRC concurred that the pediatric assessment for ages 4 yrs and older was considered adequate and deferral of studies for ages 6 months to 4 years was appropriate because the product was ready for approval in adults.

PeRC concurred that a deferred study (PREA PMR) should be required to provide a pharmacokinetic analysis of spinosad and of benzyl alcohol.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

Proprietary name: DMEPA review of Oct 22nd, 2010 states that the proposed proprietary name, Natroba, is vulnerable to medication errors (b) (4)

There are no outstanding labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval of this application is recommended
- Risk Benefit Assessment – The benefits of using topical Spinosad formulation for the treatment of headlice have been demonstrated. There are no substantial risks raised during this development program. There is consensus from all discipline reviewers that this product has demonstrated safety and efficacy.
- Recommendation for Post marketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Post marketing Requirements and Commitments – The deferred pediatric study is considered to be a required pediatric post marketing study and should be submitted as a "Required Pediatric Assessment".

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/s/

SUSAN J WALKER
12/13/2010