

**Medical Officer's Review of NDA 22-408:
Complete Response to Complete Response Letter from FDA**

Application Type: NDA 505(b)(1)
Supporting Document #: 18
Submission Type/Number: Original-1

Letter Date: July 23, 2010
Stamp Date: July 26, 2010
PDUFA Goal Date: January 26, 2010

Established name: Spinosad
Proposed Trade Name: Natroba™ Suspension, 0.9%
Therapeutic Class: Anti-lice product
Applicant: ParaPRO
Priority Designation: Standard

Formulation: Suspension
Dosing Regimen: One 10 minute application: if live lice seen, an additional application
7 days after first application
Indication: Topical treatment of head lice infestations
Intended Population: Four years of age and older

Reviewer Name: Patricia C. Brown, M.D.
Team Leader: Gordana Diglisic, M.D.
RPM: Dawn Williams
Review Start Date: September 8, 2010
Review Completion Date: December 9, 2010

EXECUTIVE SUMMARY

The submission dated July 23, 2010 contains the applicant's complete response to a complete response letter issued by the Division on November 18, 2009.

The original application was submitted January 21, 2009. The applicant, ParaPro Pharmaceuticals, submitted a 505(b)(1) application for Tradename (spinosad) Suspension, 0.9%. The proposed indication is topical treatment of head lice infestations in patients (b) (4). The active ingredient, spinosad, is a new molecular entity which is not marketed as a drug in the United States.

Tradename (spinosad) Suspension, 0.9% was demonstrated to be statistically superior to an active comparator NIX (permethrin 1%) in each of two well-controlled pivotal, Phase 3 trials. In these trials the spinosad product was applied for 10 minutes. A second application was made one week later if live lice were seen. NIX was used as labeled. Safety was evaluated in the two pivotal trials. Supportive safety data is also available from nine other Phase 1 and Phase 2 trials. In the pivotal Phase 3 trials, the three most common adverse events (application site erythema, ocular hyperemia, application site irritation) were local and the rate for these was less than that for the active comparator, NIX. In the clinical development program, no deaths occurred, and three serious adverse events, not considered related to study drug, occurred among those exposed to spinosad formulations. (Please see Clinical Review of the original NDA, dated October 30, 2009.)

After review of the original NDA by the various disciplines, the action taken was a Complete Response on November 18, 2009. The reasons for this action included the following:

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 their 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.

To address the first deficiency, items # 1 A through D, in the FDA complete response letter, the applicant relies on existing clinical, pharmacokinetic, CMC, and nonclinical information to support the safety and efficacy of Tradename (spinosad) 0.9% Suspension as a single active ingredient medication. The applicant states that their intent was that benzyl alcohol would not be an active ingredient. The applicant also makes a reasonable argument for benzyl alcohol as a legitimate component of the formulation.

To address the second deficiency regarding pk data, [REDACTED] (b) (4)

[REDACTED] The data obtained by the applicant was in healthy subjects under age 4. Since normal skin is a poor surrogate for diseased skin, "...The Division of Clinical Pharmacology has maintained that for topically applied products, bioavailability testing must be performed in subjects with the disease of interest..." (Clinical Pharmacology Review of NDA (22-408) Resubmission)

To address the third deficiency, the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. From the CMC perspective, this NDA is recommended for approval.

Regulatory Background:

A Complete Response Letter was issued November 18, 2009. With a letter dated December 29, 2009 the applicant requested a Type A meeting to discuss their response to the Complete Response Letter. The applicant submitted a briefing document dated January 22, 2010 for a Type A meeting. At the March 25, 2010 a Type A, post-action meeting the Agency indicated that further clarity was requested regarding the following principal issues (presented as excerpts of the meeting minutes that were sent to the applicant on 4/9/10):

1. Whether the presence of benzyl alcohol in the ParaPRO product is a formulation necessity, that is, must the product be formulated in benzyl alcohol? Are there data suggesting that the product cannot be formulated in a benzyl alcohol-free vehicle? Your intent that [REDACTED] (b) (4) cannot be the sole basis for determining that the benzyl alcohol is an inactive ingredient.
2. The scientific data upon which your assertion that benzyl alcohol be considered an inactive ingredient is based. We would like your perspective on the vehicle response rates and the inconsistency in these rates in the following studies:
 - a 22% and 89% treatment success rate for the vehicle in phase 2 study SPN-201-05 at days 7 and 14, respectively;
 - a 49% and 26% treatment success rate for the vehicle in phase 2 study SPN-202-06 at days 7 and 14, respectively.

Meeting Discussion:

The applicant noted that study SPN-202-05 had a different design than study SPN-202-06, including the number of treatments and combing which led to

differences in efficacy results for benzyl alcohol. The Agency requested that the applicant utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. Such an estimate may provide information to evaluate the contribution of spinosad over that of benzyl alcohol (vehicle).

3. Your methodology used to determine the benzyl alcohol exposure to the head louse and to the patient

The applicant responded with a submission dated April 13, 2010 containing responses to the FDA questions. The applicant's response discussion included:

- Document summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation
- Statistical analysis conducted to estimate the effect of benzyl alcohol in the ParaPRO formulation

Current Submission:

On July 23, 2010 the applicant submitted a "complete response to FDA's Complete Response Letter dated November 18, 2009," containing the following:

1. Response to FDA statement 1 in the complete response letter:

The applicant's response discussion includes:

- Statistical analysis (Appendix 2) conducted to estimate the effect of benzyl alcohol in the ParaPRO formulation
- Document (Appendix 3) summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation

For items # 1 A through D, in the FDA complete response letter, the applicant proposes to rely on existing clinical, pharmacokinetic, CMC, and nonclinical information to support the safety and efficacy of the ParaPRO product as a single active ingredient medication

2. Response to FDA statement 2 in the complete response letter:
3. Response to FDA statement 3 in the complete response letter:
4. A. Updated labeling, carton packaging, and bottle label
B. A new proposed proprietary name request
5. Safety update

Discussion:

1. Response to FDA statement 1 (below) in the complete response letter:

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)

The applicant's response discussion includes:

- Statistical analysis conducted to estimate the effect of benzyl alcohol in the ParaPRO formulation
- Document summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation

At the Post-Action meeting of March 25, 2010, the Agency requested that the applicant utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. The applicant has responded to this by providing a statistical report in Appendix 3 of the current submission. This report is evaluated in statistical review (of supporting document 15) dated May 19, 2010. A summary of the statistical comments is provided in the current document in "Statistics" under "Significant Findings from Other Review Disciplines."

The applicant responds to the suggestion that their spinosad drug product has two active ingredients by arguing that although Ulesfia Lotion was approved with 5% benzyl alcohol as the active ingredient, the (b) (4) benzyl alcohol in Tradename (spinosad) 0.9% Suspension is not an active ingredient principally because the intent of the formulation (b) (4) for the intended active ingredient spinosad.

The applicant submits the following three items (in bold) to support the assertion that benzyl alcohol is a necessary inactive ingredient.

A. The intent of having benzyl alcohol in the Spinosad product formulation is (b) (4) as the alcohol of choice with minimal interference to hair and scalp quality.

The applicant states that they purchased the formulation and related technology from Johnson and Johnson. The applicant asserts that typical hair treatment formulations are aqueous based products. For the Tradename (spinosad) 0.9% Suspension drug product, (b) (4) spinosad, the active ingredient. The applicant states that benzyl alcohol is preferred (b) (4) because it is a USP/NF ingredient (b) (4)

A search of the FDA website Inactive Ingredient Search for Approved Drug Products (<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>) performed by this reviewer on

9/23/2010) reveals 87 approved drug products containing benzyl alcohol at concentrations up to 10.96%, in a product for intramuscular injection, and up to 50%, for a topical gel product.

The applicant states that they never intended benzyl alcohol in the product to be an active ingredient.

Per 21CFR210.3(b)7, *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.

Clinical Comment for Statement A:

The applicant's intent is a legitimate factor to consider in evaluation whether benzyl alcohol is an active ingredient in the drug product, Tradename (spinosad) 0.9% Suspension.

B. Benzyl alcohol is a formulation necessity (b) (4)

The response to this is based on information provided in Appendix 3 of the current submission and consists of a document summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation.

The applicant asserts that typical hair treatment formulations are aqueous based products. For the Tradename (spinosad) 0.9% Suspension product (b) (4) were needed to (b) (4) spinosad, the active ingredient.

The formulation evaluated in the spinosad NDA 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. (b) (4)

(b) (4)

(b) (4)

pH Effects:

The applicant states that net, the pH can be adjusted in the range of 5.0-7.5 for the spinosad formulations. (b) (4)

Therefore, pH is not likely to have a significant influence to cause an increase in spinosyn D solubility in the pH range used for the spinosad formulation.

Clinical Comments for Statement B:

A reasonable argument appears to be made for benzyl alcohol as a legitimate component of the formulation.

C. The volume exposure to benzyl alcohol in the Ulesfia treatment versus the Spinosad product treatment is substantially different.

The applicant states that in the complete response letter it was noted that the spinosad product contained (b) (4) benzyl alcohol versus Ulesfia Lotion at 5% with a potential impression that there is higher exposure to benzyl alcohol from the spinosad product than from Ulesfia Lotion.

The applicant calculated the benzyl alcohol exposure to the patient, for Tradename (spinosad) 0.9% Suspension and Ulesfia Lotion based on the directions for use.

(b) (4)

Table 3: Calculation of Benzyl Alcohol Exposure to Patient

	Spinosad product	Ulesfia
Specific Gravity (g/mL)		(b) (4)
Weight of bottle contents (g)		
Benzyl Alcohol (BA) content (%)		
BA content (g/bottle)		
Bottles per application		
Required applications		
Total bottles used		
Total BA exposure per application		
Total BA per Treatment		

Based on applicant's table in submission dated April 13, 2010

The applicant argues based on the above calculations that the exposure to benzyl alcohol in Tradename (spinosad) 0.9% Suspension will be less than that for benzyl alcohol in Ulesfia, for all Ulesfia treatment regimens except for the one with the shortest hair (0-2 inches).

However, the argument presupposes that there will only be one treatment with Tradename (spinosad) 0.9% Suspension. Tradename (spinosad) 0.9% Suspension will be labeled for one treatment and a second treatment one week (7 days) later if live lice are seen. Then by the above calculations exposure to benzyl alcohol in the spinosad product will be higher than that than in Ulesfia Lotion for treatment regimens for hair lengths 0-2 inches and 2-4 inches.

Additionally it may be argued that patient exposure to benzyl alcohol in the formulation is more a function of the degree to which the scalp is made wet by the product. Once there is a layer of product at the scalp surface, excess volume of product will only increase exposure of non-vital hair shafts (and lice.) In this type of situation, differing concentrations 5% versus (b) (4) might be expected to play a larger role in patient exposure.

Clinical Comment for Statement C:

The applicant does not make a convincing argument that the volume of exposure to benzyl alcohol in the Ulesfia treatment is substantially different (more) than that in Tradename (spinosad) 0.9% Suspension.

2. Response to FDA statement 2 (below) in the complete response letter:

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 their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.

(b) (4)

The applicant argues that compared with Ulesfia Lotion, providing PK data on subjects 6 subjects from 6 to 36 months, with Tradename (spinosad) 0.9% Suspension PK data has been provided on 8 subjects ages 6 to 24 months. Ulesfia Lotion received a use claim for subjects 6 months and older and ParaPRO has been asked to provide more PK data, representing to ParaPRO a non-level playing field.

The important distinction is that the subjects studied for Ulesfia Lotion had active head lice infestation with at least 3 live lice and all subjects were observed to have at least moderate pruritus and excoriation of the scalp. The PK study performed by ParaPRO involved 8 healthy subjects without lice infestation.

At the pre-IND meeting May 12, 2003, the Agency stated that:

Pediatric PK studies should be done in patients with head lice infestation as the presence of scalp irritation could result in increased systemic absorption. This would mirror the use of the final marketed product and would be a better measure of true systemic exposure upon use since it will maximize dermal/scalp absorption.

Although patients with lice can be asymptomatic, pruritus is common¹. Pruritus may take 2 to 6 weeks to develop after first exposure. This reflects an immunologic response thought to be to components of louse saliva or anticoagulant. Common findings include excoriations, erythema, pyoderma, and scaliness of the scalp and posterior neck.² These findings represent alterations of the skin barrier, which can affect topical drug absorption. Thus it is important to have PK data in subjects having lice infestation. Please also see Clinical Pharmacology Review of NDA 22-408 Resubmission.

Clinical Comment:

(b) (4)

3. Response to FDA statement 3 (below) in the complete response letter:

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

Details of CMC information needed as found in complete response letter of November 18, 2009

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 cetareth-20 and stearylalkonium chloride.

¹ Ko CJ and Elston DM. Pediculosis. Continuing Medical Education. J Am. Acad. Dermatology 2004;50:1-12.

² Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bologna JL and Jorizzo JL, Elsevier, Inc. © 2009.

- 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 spinosyn 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 (b) (4) on drug product quality:
- 1) Data indicating when the (b) (4) starts during storage and whether the storage conditions have any effect (b) (4);
 - 2) Data to demonstrate that content uniformity for the (b) (4) drug product is re-established after shaking; and
 - 3) A description for 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.

In the current submission, the applicant has provided information in response to each of the requests detailed above. This information has been reviewed by the chemistry reviewer, Zhengfang Ge, Ph.D., Chemistry Review dated September 28, 2010. According to her review:

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.

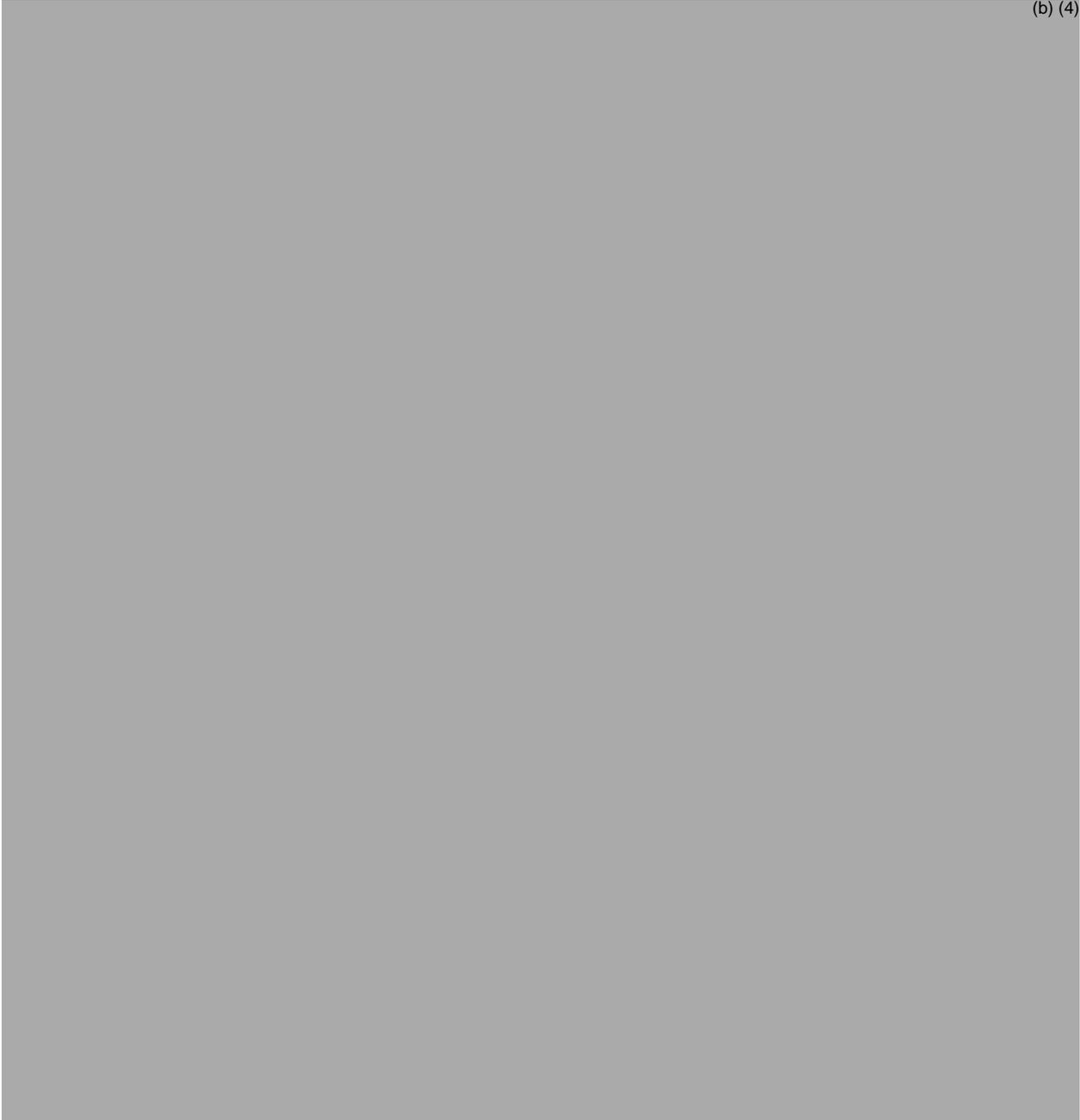
All facilities have “Acceptable” site recommendations from the Office of Compliance.

Clinical Comment:

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the spinosad drug substance and the drug product.

4. A. Updated labeling, carton packaging, and bottle label

The applicant submitted updated labeling, carton packaging, and bottle label for Agency comment. DMEPA review of carton and bottle label was pending at time of closure of this review.



(b) (4)

(b) (4)



Physician's Insert Labeling: at the time of closure of this review (12/8/2010) physician's insert labeling was under negotiation.

4. B. A new proposed proprietary name request

The complete response letter of November 18, 2009 included the following:

(b) (4)



On July 23, 2010 as part of 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.

The Division of Dermatology and Dental Products (DDDP) requested a review of the proprietary name from the Division of Medication Error Prevention and Analysis (DMEPA). Please see Proprietary Name Review for Natroba (Spinosad) Suspension, 0.9%, dated October 22, 2010.

A promotional assessment of the proposed name, Natroba, was performed by DDMAC and the name was determined to be acceptable. The Division of Dermatology and Dental Products and the Division of Medication Error Prevention and Analysis concurred.

A safety assessment was performed by DMEPA and it was determined that the proposed name, Natroba, is vulnerable to name confusion with the proposed proprietary name for a pending application. This name confusion could lead to medication errors. Comments sent to the applicant (October 22, 2010) included the following:

...Natroba and the pending proprietary name are orthographically similar and share overlapping product characteristics. Therefore, at this time, the acceptability of the proposed proprietary name, Natroba, is dependent upon which application is approved first. If the Agency approves the Natroba NDA first, we will recommend the other applicant seek an alternate name. If the other application is approved prior to your application, then you will be requested to submit another name.

5. Safety update

The applicant states that there is no new safety information to report.

Significant Findings from Other Review Disciplines

CMC

From the Chemistry Review, dated September 28, 2010:

Drug Substance:

The proposed drug substance, spinosad, is a new molecular entity, and a fermentation product produced by the actinomycete, *Saccharopolyspora spinosa*. Spinosad contains two components, spinosyn A and D. The applicant cross referenced to DMF 17795 held by Dow AgroSciences LLC (Michigan, USA) for CMC information of spinosad. The DMF was reviewed and found adequate to support the NDA. In this amendment, the applicant provided an updated regulatory specification for the drug substance which is acceptable.

Drug Product:

The proposed drug product, Natroba (spinosad) suspension 0.9% w/w, is a light orange colored, slightly opaque, viscose liquid. (b) (4)

The product is packaged in a 4 ounce,

white, HDPE bottle with a white, child resistant, snap top cap closure and spout. The drug product contains (b) (4) benzyl alcohol. In the Agency's CR letter to the applicant, the clinical division requested the applicant to provide information to support approval of the proposed product with a single active ingredient, spinosad, and to demonstrate why benzyl alcohol is not an active ingredient. Based on the information submitted in 23-July-2010 amendment, the clinical division made the decision that benzyl alcohol is an excipient. Therefore, the CMC information for benzyl alcohol as reviewed in CMC Review #1 is adequate. In this amendment, the applicant updated specification for the drug product according to the Agency's request in the CR letter and during the teleconference held on 20-Sep-2010. The applicant also adequately addressed (b) (4) issues raised during the previous review circle. Based on the information provided in this amendment, the proposed 36 months expiration period is acceptable.

The applicant provided revised labeling according to the CMC comments and the revision is acceptable.

(CMC) Recommendation and Conclusion on Approvability

This NDA has *now* provided sufficient/adequate information to assure the identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The labels and labeling (Description and How Supplied sections) have adequate information as required.

Therefore, from the CMC perspective, this NDA is recommended for approval. (See CMC Review dated September, 28, 2010, Zhengfang Ge, Ph.D., Branch IV, Division of Drug Quality Assessment II, Office of New Drug Quality Assessment)

Animal Pharmacology/Toxicology

Please see pharmacology/toxicology Memorandum by Jianyong Wang, Ph.D., dated September 30, 2010.

From the Pharmacology/toxicology Memorandum:

Discussion and conclusions (excerpted):

The Agency has determined that benzyl alcohol, (b) (4) in the Natroba product, is not a second active ingredient. No new nonclinical information is required at this time. The NDA for Natroba Suspension (0.9% spinosad) is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label discussed in the next section are incorporated into the Natroba Suspension label. No nonclinical postmarketing studies are recommended for this drug product.

It is noted that the Maternal Health Team proposed further changes to the suggested wording for Section 8.1 of the Natroba label. An additional sentence was added and became the second sentence in the first paragraph of Section 8.1: “Studies in humans did not assess for the absorption of benzyl alcohol contained in Natroba Suspension.” This proposed change obtained concurrence from clinical during the final labeling meeting and it is also acceptable from a pharmacology/toxicology perspective.

Clinical Pharmacology

From the Complete Response Letter of November 18, 2010:

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 their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.

(b) (4)

See Clinical Pharmacology Review of NDA Resubmission by CAPT E. Dennis Bashaw, Pharm.D, OCP, DCP III, dated October 6, 2010. From the Clinical Pharmacology Review:

The sponsor cites a “precedent” from the approval of the Ulesfia (NDA 22-129) application where the product received a pediatric indication for subjects 6 mos and older with a seemingly lesser amount of information...

The sponsor goes on to state (b) (4) that they are concerned with “a level playing field” for their product.

FDA Discussion

The FDA supports and strongly encourages a “level playing field” for sponsors. However, in doing so we must be cognizant that the primary difficulty in their comparison to the Ulesfia data is that in the Ulesifa NDA (as indicated in both the approved label and in the NDA reviews available on Drugs@FDA) the study was done in patients with lice infestation. We draw attention to the first paragraph of FDA’s comment #2 where it is made quite clear that we are concerned not only with the small numbers but the lack of information in subjects with lice infestation. The comment goes on to discuss our concerns in this area “*The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp*”

In comparison, the six subjects below the age of 2 cited in the Ulesfia dataset did have concomitant lice infestation. Thus, in fact, instead of “a level playing field” the sponsor is “mixing apples and oranges” or equating data in healthy subjects with those with lice infestation which does not represent “a level playing field” towards Ulesfia. The sponsor did conduct a trial in children with lice infestation, but the cut-off in that study was 4yrs of age...

Conclusion

CR Letter Item 2

(b) (4) The issue cited in the CR letter was related to the lack of in vivo pk data in subjects with active lice infestation below the age of 4yrs. The data cited by the sponsor vis a vis the Ulesfia approval overlooks the fact that the Ulesfia data was collected in subjects with an active infestation. This point is clearly indicated in the current Ulesfia package insert. The Division of Clinical Pharmacology has maintained that for topically applied products, bioavailability testing must be accomplished in subjects with the disease of interest as normal skin is a poor surrogate for diseased skin and is not accepted as such by the Division and Office of Clinical Pharmacology.

Statistics

According to the statistical reviewer, the applicant’s statistical analysis (Appendix 2 of Complete Response submission) is the same as that presented in the statistical report (submitted April 19, 2010). That report was reviewed by the statistical reviewer, May 19, 2010 and the reader is referred to the review for comments. Please see NDA Statistical Report Reviews dated August 25, 2010 and May 18, 2010, Carin Kim, Ph.D., DBIII.

Background:

Ulesfia (NDA 22-129) was approved for the treatment of head lice while NDA 22-408 was under review. From the statistical review:

Ulesfia’s active ingredient is benzyl alcohol at a concentration of 5%. The sponsor’s product (spinosad (b) (4)) contained benzyl alcohol at a higher concentration (b) (4). Because neither of the Phase 3 studies contained a benzyl alcohol treatment arm, the data from the Phase 3 studies cannot be used to discern the contribution of spinosad.

A Type A post-action meeting was held on March 25, 2010. During the meeting discussion, the Agency requested that the applicant utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. It was hoped that this estimate would provide information to evaluate the contribution of spinosad over that of benzyl alcohol.

The applicant responded with a submission dated April 13, 2010 containing responses to the FDA questions. The applicant’s response included a statistical analysis using the

results of Study SPN 202-06 (not study SPN 202-05) results to predict the treatment effect of benzyl alcohol if it were to be used for two treatments as it was used in the Phase 3 trials. From the statistician's review (Conclusion and Discussion):

As for Study 201-05, this reviewer agrees with the Sponsor's conclusion (although the reviewer's arguments are different in reaching this conclusion) that Study 201-05 cannot be used to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for two treatments as it was in the Phase 3 trials.

In the statistical analysis, data from the Phase 3 studies for the ParaPRO product without nit combing were used to develop an optimized tree-diagram to predict idealized treatment results. According to the applicant, the tree-diagram was then used, along with observational data from one of the Phase 2 study, SPN-202-06, to predict idealized efficacy rates for the benzyl alcohol-vehicle. Regarding the benzyl alcohol treatment effect if it were to be used for two treatments without combing, from the statistician's review (Conclusion and Discussion):

This reviewer's position is that such information can not be extrapolated from Study 202-06 either, as the study only involved one treatment at Day 0, therefore, the sponsor's tree diagram to predict the success rate of benzyl alcohol cannot be justified....Clearly, the sponsor did not have a benzyl alcohol arm of two treatments without combing as a part of their clinical program, therefore, the sponsor's studies cannot be used to predict the efficacy for the benzyl alcohol if it were to be used for two treatments without combing.

Clinical Comment:

The applicant's statistical analysis does not support the applicant's statement, from submission of April 13, 2010, that the "...efficacy of the ParaPRO product is substantially greater than the benzyl alcohol-vehicle (2.7 times greater)."

Other Relevant Materials:

Pediatrics:

For a new drug application, 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. Studies must include data to support dosing and administration. For NDA 22-408, this would include relevant pharmacokinetic data for subjects having lice infestation from age 6 months up to 4 years. Additional pharmacokinetic study data will be needed.

Pediatric Plan:

The applicant submitted:

- Request for Waiver of Pediatric Studies on September 14, 2010

Under 21 CFR 314.55(c)(3)(i) the applicant requests a waiver of pediatric research in infants 0 to 6 months of age.

The reasons given were that

- a) Studies are highly impractical or impossible
- b) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of patients in these age groups.

- A commitment to provide pharmacokinetic data for pediatric subjects

The applicant agrees to commit to conducting a post-approval pharmacokinetic study in lice infested subjects in the 6 month to 4 year age range.

- Dates for submission for the PMR pharmacokinetic study

Protocol Submission: March (b) (4) 2011

Study Initiation: September (b) (4) 2011

Study Completion: December (b) (4), 2011

Final Study report Submission: March (b) (4) 2012

The application was presented to PeRC (Pediatric Review Committee) on September 22, 2010. The Pediatric Review Committee had the following comments.

A) The Waiver for Pediatric Studies ages 0 up to 6 months is appropriate. The Committee agreed with the reasons as provided above, but also recommended including the reason: The product would be unsafe in the pediatric age group for which a waiver is being requested. This reason would apply to the benzyl alcohol component of the Tradename (spinosad) 0.9% Suspension drug product. Language regarding safety for benzyl alcohol is being included in section 8.4 of Tradename (spinosad) 0.9% Suspension product labeling. Please see discussion of labeling in this review below under Pediatric and Maternal Health Staff.

B) A Deferral ages 6 months to 4 years is appropriate.

Because the company did not submit this information with adequate detail as part of an explicit Pediatric Plan, PeRC requested that the applicant submit a Pediatric Plan that would provide a pediatric assessment for patients ages 0 up to 4 years (including the 0 to 6 months and 6 months to 4 years of age groups).

C) The Pediatric Assessment provided by the applicant for ages 4 and older is satisfactory.

D) Regarding the deferred study (PREA PMR), pharmacokinetic data should be requested in pediatric patients with head lice 6 months to less than 4 months of age. The deferred study should be enriched with pediatric patients in the younger age and weight groups.

As developed by the clinical review team in consultation with clinical pharmacology, a suggested outline for the PREA PMR follows:

The study would be an open label study PK study of Tradename (spinosad) 0.9% Suspension under maximum use conditions in patients with an 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 pk sampling program is acceptable.

Follow Up with Applicant Regarding Pediatric Plan:

The applicant was notified that the information they had submitted regarding the pediatric deferral was insufficient. More detail was need about their proposed study that provide a pediatric assessment for patients ages 0 up to 4 years (including the 0 to 6 months and 6 months to 4 years of age groups).

On October 1, 2010 the applicant provided a draft Pediatric Plan that included:

- A) a request for a waiver from age 0 up to 6 months
- B) a request for a deferral for ages 6 months up to 4 years - This was accompanied by the following:
 - Specifically, our intent is:
 - a. To assess subjects from 6 months to 4 years of age.
 - b. To have 2 groups of 12 subjects; the first group being 6 months to 1 year of age, and the second group being 1 year to 4 years of age.
 - c. To divide equally the subjects between male and female.
 - d. To enroll only healthy subjects except for active lice infestation.
 - e. To do a Pharmacokinetic analysis on both Spinosad and BA, single dose AUC, C_{max} , T_{max} . Safety assessment will include systemic safety, vital signs, lab evaluations, local safety such as scalp and ocular irritations, pruritus, and any other adverse events.
- C) Timelines for protocol submission, study intitiation and completion, and submission of final study report.

The revised Pediatric Plan was provided to PeRC. On 10/12/10 PeRC provided an addendum to their review which stated that they now agreed with the Division to grant a deferral because the product is ready for approval in adults. The PeRC also had the following comments:

- PeRC members noted that enrollment should be clarified: pediatric patients with active lice infestation who are otherwise healthy.

- The PeRC is unsure what studies the Division will require under a PREA PMR and unless there are other safety data that can be applied to this product, a sample size of 24 (divided into 2 groups) appears inadequate.

A response was provided to these comments that noted:

- The sponsor indicated that they intended to enroll only healthy subjects except for active lice infestation
- Other safety data are available for patients 6 months to 3 years from the Phase 3 trials. In this age group safety data are available on 67 patients. When data from the PREA PMR are added, then safety data will be available on 91 patients. This will be a greater number than was asked for by the division for a similar application, Ulesfia (80 patients).

On 10/14/10 the following response was received:

Your responses are noted and will be forwarded to PeRC members. The comments provided were done so as advisory to the Division. The PeRC review this product concluded with the review of the sponsor's submitted pediatric plan. The Division is free to take action on the product when ready.

Conclusion Regarding PMR:

It is this reviewer's opinion that the PMR as proposed above will be adequate to fulfill clinical information needs for safety.

Pediatric and Maternal Health Staff:

Regarding the Pediatric Use, Pregnancy, and Nursing Mothers subsections of labeling, consultation was obtained with the Pediatric and Maternal Health Staff, including the PMHS-Pediatric Team and the PMHS-Maternal Health Team. Please see Pediatric and Maternal Health Staff Review dated October 6, 2010.

The Pediatric and Maternal Health Staff (PHMS) made the following 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".

PHMS recommendations #1 and #2 have been incorporated as described above, under pediatrics. Additionally, the sponsor will be notified 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".

PHMS recommendation regarding pregnancy and nursing mothers are incorporated into proposed labeling as follows:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies with NATROBA Topical Suspension in pregnant women. Studies in humans did not assess for the absorption of benzyl alcohol contained in NATROBA Topical 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...

8.3 Nursing Mothers

Spinosad, the active ingredient in NATROBA Topical Suspension is not systemically absorbed; and therefore, will not be present in human milk. However, NATROBA Topical Suspension contains benzyl alcohol, which may be systemically absorbed through the skin, and the amount of benzyl alcohol excreted in human milk with use of NATROBA Topical Suspension is unknown. Caution should be exercised when NATROBA Topical Suspension is administered to a lactating woman. A lactating woman may choose to pump and discard breast milk for 8 hours after use to avoid infant ingestion of benzyl alcohol.

PHMS recommendations regarding pediatric labeling are as follows:

8.4 Pediatric Use

The safety and effectiveness of NATROBA Topical Suspension have been established in pediatric patients 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 Topical Suspension is not recommended in pediatric patients below the age of 6 months because of the potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.

NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions 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 infants. 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)].

The pediatric labeling recommended by PHMS includes the statement: “NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions and death, particularly in pediatric patients.” In the opinion of this reviewer this statement may be inappropriate for situation of use as labeled for Tradename (spinosad) 0.9% Suspension. Benzyl alcohol used as preservative in saline flush solutions has been associated with 16 neonatal deaths. The deaths occurred in pre-term neonates weighing 2500 grams who had central intravascular catheters flushed periodically each day with bacteriostatic saline containing 9 mg/ml benzyl alcohol. Estimates of daily intake of benzyl alcohol ranged from 99 to 405 mg/kg/day.³ It should be noted that the intended population for the current application is children ages 4 and older. Proposed labeling also provides for short topical application (10 minutes) to a limited part of the body (hair and scalp) and for one and sometimes two treatments one week apart. It is highly unlikely, for the intended population and with topical and not parenteral application, that blood levels of benzyl alcohol would be achieved that are high enough to cause serious adverse reactions or death.

Recommended labeling that would be appropriate to the expected level of risk with use of Tradename (spinosad) 0.9% Suspension includes the following modifications (deletions = ~~strikeout~~; additions = underline):

~~_____~~ (b) (4)
(b) (4) Neonates could be at risk for gasping syndrome if treated with NATROBA Topical Suspension because it contains benzyl alcohol. Intravenous administration of products containing benzyl alcohol has been associated with neonatal gasping syndrome. 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 infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The modifications recommended above would make this section of labeling for Tradename (spinosad) 0.9% Suspension more consistent with the labeling for Ulesfia, a product currently approved for treatment of head lice and containing 5 % benzyl alcohol.

³ Neonatal Deaths Associated with Use of Benzyl Alcohol – United States: CDC; MMWR 1982; 31:290-291.

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/s/

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12/09/2010

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12/09/2010