

Clinical Pharmacology Review of NDA Resubmission

PRODUCT (Generic Name):	Spinosad 0.9%
PRODUCT (Proposed Brand Name):	TRADENAME
NDA:	22-408
TYPE:	505(b)(1)
PROPOSED INDICATIONS:	pediculocide
SUBMISSION DATES:	7/23/10
SPONSOR:	ParaPro Pharmaceuticals
REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D.
OCP DIVISION:	DCP III

Spinosad 0.9% is being developed for the control of human head lice (b) (4). An original NDA for this product was submitted in Jan. 2009 and a complete response letter was issued on Nov. 18th, 2009. Two issues presented in the letter dealt with the pharmacokinetics of benzyl alcohol (item 1 b) and dermal absorption in pediatric patients (item 2).

FDA CR LETTER ITEM 1

Item 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".

Sponsor's Response

For items #1 A thru #1D in the Agency's Complete Response Letter, we propose to rely on the existing clinical, pharmacokinetic, CMC, and nonclinical information to support the safety and efficacy of the ParaPRO product as a single active ingredient medication.

FDA Discussion

With regards to item 1b the sponsor has essentially elected to not respond, 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. The issue of whether or not benzyl alcohol is or is not an active ingredient is deferred to the Medical Reviewer.

FDA CR LETTER ITEM 2

Item 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)

Sponsor’s Response

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 recently approved head lice medication Ulesfia received a use claim for subjects 6 months and older and provided PK data for only 6 patients ranging in age from 6 to 36 months. ParaPRO exceeded that number by 33%, providing PK data on 8 subjects in an even younger age range from 6 to 23 months”

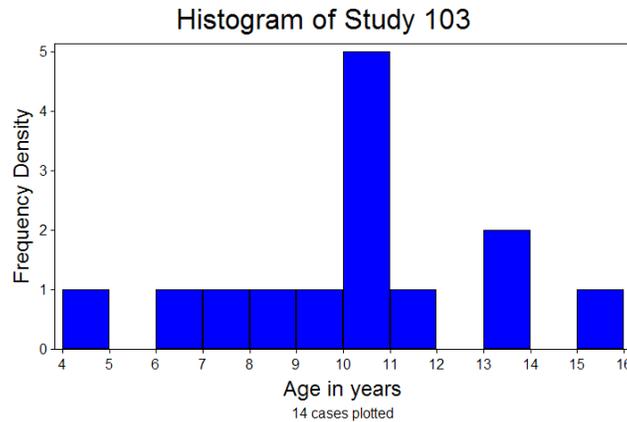
The sponsor goes on to state that they (b) (4) but that they are concerned with “a level playing field” for their product.

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 Ulesfia 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. This comment then 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 (see below).



In fact, our acceptance of this data with regards to the proposed 4 yr cut-off is consistent with our acceptance of the limited data cited with Ulesfia in the younger age range. The difference here is the fact that the Ulesfia data, again, was in patients and not healthy subjects.

Conclusion

CR Letter Item 1

The issue of whether or not benzyl alcohol is or is not an active ingredient is deferred to the Medical Reviewer. Should it be decided that it is an active ingredient, then the Division of Clinical Pharmacology will provide input as to the type of study needed to address item 1b of this comment.

CR Letter Item 2

The sponsors proposal (b) (4) is unacceptable. 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.

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/s/

EDWARD D BASHAW
10/06/2010