CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75014

MEDICAL REVIEW

Medical Officer Summary
September 14, 1999

ANDA 75-014
Drug Product: Permethrin Crème Rinse, 1%
Sponsor: Alpharma

This in vivo bioequivalence study was reviewed in OGD and then received a secondary medical review in the Division of Dermatologic and Dental Drug Products. A statistical review was also completed. In addition, the findings were discussed at a meeting initiated by the Division of Over the Counter Drug Products on the recommended study design for this type of study. The study was found acceptable and the product deemed to be bioequivalent to the reference listed drug.

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Medical Officer Review
March 30, 1999

ANDA 75-014
Drug Product: Permethrin Lotion, 1%
Sponsor: Alpharma U.S. Pharmaceuticals
Reference Listed Drug: Nix ® Crème Rinse, Warner Lambert Company

Title: Alpharma 1% Crème Rinse vs. Nix Bioequivalence Study
Study Number: Alpharma and FEST – AL-218
Phoenix Project Number 980777

Study Site: Community clinic of Ticantiki, Ticantiki, Comarcas de San Blas, Republic of Panama

Study Objective: The objective of the study was to compare the safety and efficacy of 1% Permethrin Crème Rinse (Alpharma) vs. Nix ® Crème Rinse in the treatment of head lice for the purpose of establishing therapeutic equivalence between the test and reference products.

Study Design: This was a randomized, double-blind, parallel study. A total of 111 subjects were enrolled into the study and randomized into two treatment groups using a computer generated list. Fifty-six were randomized to each arm.

Inclusion/exclusion criteria:
Patients who entered the study met the following criteria, which were set out in the protocol in the following words:
1. Patient or guardian has read, understood, and signed appropriate informed consent.
2. Patient has an active infestation with *Pediculosis humanus capitis*, the human head louse, with at least 6 live adult lice or nymphs, and at least 20 viable appearing eggs.
3. Patient will be available and willing to report for follow-up examinations.
4. Patient agrees not to use any other pediculicides or medicated hair-grooming products during the duration of the study.
5. Patient is otherwise healthy, non-febrile, and is not suffering from an infection likely to require antibiotic therapy during the study period. These criteria will be ascertained prior to enrollment by a visiting physician from the Ministry of Health, Republic of Panama, assisted by the local resident health provider/midwife.

Patients were excluded if they met the following criteria:
1. Patient or guardian has not signed informed consent.
2. Patient is suffering from a condition likely to require medical attention, including administration of oral or systemic antibiotics, oral or systemic corticosteroids, or any other treatment which in the opinion of the investigator and visiting physician could influence the results of the study.
3. Patient is pregnant or lactating.

4. Patient is less than 2 years of age.
5. Patient is suffering from an abnormal scalp condition not usually associated with head louse infestation, e.g., seborrheic dermatitis, alopecia, tinea capitis, contact dermatitis, severe pyoderma, or lymphadenopathy.
6. Patients with very short (shaved) hair.
7. Patients whose hair is too thick or too long to be saturated with two containers of test product.
8. Patient will not be available for follow-up visits.
9. Patient has been treated with a systemic antibiotic within the previous week.
10. Patient has used a pediculicide within the previous two weeks.
11. Patient has used a medicated shampoo within the previous week.
12. Patient has been previously empanelled in this study.
13. Patient has a known hypersensitivity to natural pyrethrins, pyrethroids, chrysanthemums or roses.

Randomization: Eligible subjects were randomly assigned to one of the two treatment groups: NIX Crème Rinse, Warner Lambert Co. and 1% Permethrin Crème Rinse, Alpharma USPD. The sponsor prepared the randomization code with appropriate blocking. The code was placed on the right wrist of the subject.

Study Conduct:

Pretreatment: Prior to treatment, trained personnel collected 10 live lice or nymphs from the patients' heads and clipped 10 hairs each containing a viable egg. These were stored in glass vials until egg hatching was done. Subjects were shampooed with Prell and the hair was rinsed and dried. Treatment with 1% Permethrin crème rinse was applied by trained staff. It was left in place for 10 minutes and then thoroughly rinsed out.

Post treatment: The rinse water was processed for louse counts, and 10 hairs with attached eggs were collected. Thirty to 60 minutes after treatment, the skin and scalp of study subjects were examined for signs and symptoms of erythema, burning, numbness, stinging, or other evidence of the effects of treatment.

Study visits: Day 1 – a home visit was made 18 to 24 hours after treatment to evaluate the skin and scalp.
Day 7 – subjects were examined for the prescence of live adult lice or nymphs as well as new viable eggs.
Day 14 – subjects were thoroughly examined for the presence of live adult lice or nymphs as well as viable eggs.

Endpoints:
Primary – Subjects were scored at Day 14 as:
Treatment Failure (live lice at any stage day 7 or >5 adult lice or any nymphs at day 14)
Treatment Success (day 7 and 14, no lice or viable eggs)
Re-infestation (day 7 no lice or viable eggs, day 14 adult lice)

Treatment Success was defined as above. Treatment failure was defined as both treatment failure and re-infestation (see above). This was designated as the measure of primary efficacy in the protocol.

Treatment Cure was defined as both treatment success and re-infestation as described above. Subjects who scored as treatment failure were defined as having no treatment cure.

Secondary – These included the following endpoints:

Pediculicidal Activity – success was defined as no viable lice or eggs at Day 7.
Ovicidal Activity – this was defined as the change from baseline in the number of eggs (of the 10 collected) hatched at day 14 calculated as a hatch rate.
Re-infestation Rate – this was calculated as the proportion of subjects successfully treated at day 4 who had adult lice at day 14.

Results:

Enrollment: One hundred-eleven subjects were enrolled into the study; 56 were randomized into the Nix Creme Rinse arm, and 55 into the 1% Permethrin Alpharma Crème Rinse arm.

Demographics: All the subjects enrolled except one were of the Kuna race and had straight hair. No statistically significant differences were detected in any demographic parameters (sex, age, weight, height, race, hair texture, curliness, and length) between the treatment groups. Fifty-three (47.7%) were male and 58 (52.3%) were female. The mean age was 10.5 +−7.1 (range, 3 – 64) and the mean weight was 56.8 +_ 20.8 (range 25 – 122).

Protocol Adherence: The following definitions are put forth in the analysis plan:

A. Protocol violation

1. An authorization of randomization when it is known before or after randomization that the patient is ineligible according to inclusion or exclusion criteria set forth in the study.
2. Missing any of the follow-up visits.
3. Use of any other pediculocides or medicated hair grooming products during the duration of the study.

B. Protocol deviation

1. Failure to return within the accorded window for
   Day 7 evaluation: Day 7 +/- 1 day
   Day 14 evaluation: Day 14 +/- 2 days

Analysis Population: Intent-to Treat (ITT) population includes all randomized subjects who received medication, were evaluated at baseline (Visit 1), and had at least one

follow-up visit. According to the statistical plan this is the only population that is considered in the report.

Medical Officer Note: An ITT population is not used for bioequivalence studies to evaluate the primary endpoint. An efficacy valid population, subjects who complete therapy and are evaluated at each follow-up visit, is considered the analysis group.

Protocol Violations:

There were 10 protocol violations listed by the sponsor involving 9 subjects. The violations are listed below:

049 Nix – did not meet infection inclusion criteria

Medical Officer Note: This subject should have been excluded from all the analyses but it doesn't seem that this occurred.

076 Alp – missed Visit 3
055 Nix – missed Visit 3
106 Nix – missed Visit 3
084 Alp – missed Visit 2, no score day 14 (< 5 lice)

* These 4 subjects were excluded from all of the 1° efficacy analyses and the secondary analysis of re-infestation.

006 Alp – missed Visit 2
026 Alp – missed Visit 2
076 Alp – missed Visit 2
084 Alp – missed Visit 2
020 Nix – missed Visit 2

* These subjects were not considered eligible for the 2° analysis of treatment success at Day 7.

Protocol Deviations:

Subject 084 (Alph) had no score on Day 14 (<5 lice) and missed Visit 2 on Day 7. This subject's protocol deviations were already included in the protocol violations listed above.
Subject 085 (Nix) used medication that according to the investigator and visiting physician was likely to influence the results of the study.

Medical Officer Note: The summary listing of subjects notes that subject 085 "...took erythromycin during the study. This may have killed his lice or rendered eggs sterile. I consider 14 day results invalid." This subject was considered eligible for all analyses

despite the fact that this would be considered a protocol deviation according to the statistical plan.

Efficacy Evaluation:

Primary Endpoints

Clinical Response

OUTCOME	TREATMENT SUCCESS	
	Alpharma	Nix
Success	46	41
Failure	7	10
Re-infestation	0	3
Not Done	1	2
Unknown	1	0

Treatment Success

The sponsor used an ITT population to calculate treatment success (the primary endpoint according to the protocol) as well as treatment cure.

OUTCOME	Alpharma	Nix	p-value
Success	46	41	0.15
Failure	7	3	

The two treatments were found to be similar statistically for treatment success using the Chi-square test (p=0.15). However, they were not therapeutically equivalent in proportions of successfully treated, -0.11, 90% CI -0.25, -0.03. The same results were obtained using a logistic regression, OR=2.1, 90% CI 0.9, 4.9.

Treatment Cure

OUTCOME	TREATMENT CURE	
	Alpharma	Nix
Cure	46	44
No Cure	7	10

Treatment cure was defined in the final report and includes both treatment success and re-infestation. Using a Chi-square test, both treatments were similar, p=0.45. They were found to be therapeutically equivalent using the proportion of successfully cured, -0.05, 90% CI -0.19, -0.08 or the logistic regression OR=1.5, 90% CI 0.5, 4.3.

Medical Officer Note: The sponsor used an ITT population in evaluating bioequivalence. An efficacy valid population is used for this type of analysis. In addition, the primary endpoint defined in the protocol, treatment success, does not meet the equivalence

criteria applied by the sponsor in the analysis. Treatment cure is introduced in the final report as the primary endpoint. Using this parameter, the sponsor is able to show equivalence for the proportion successfully cured.

Medical Officer Analysis – The data necessary to calculate the efficacy valid treatment success was available in the submission. Using this information, the following data was subjected to an equivalence analysis.

	Alpharma	*Nix*		*Alpharma*	*Nix*
Success	*44*	*38*	***Cure***	*44*	*41*
Total	*51*	*51*	*Total*	*51*	*51*
Delta	*11.76*		*Delta*	*5.88*	
90% CI	*-2.99, 26.52*		*90 % CI*	*-8.18, 19.95*	

This demonstrated that the endpoint of treatment success did not meet equivalence criteria in that Alpharma's product was more efficacious. When the endpoint of treatment cure was used to evaluate bioequivalnece the two products met the equivalence intervals. This included the cases that showed a cure a day 7 and re-infestation at day 14.

Secondary efficacy endpoints

Pediculicidal Activity at Day 7

Alpharma and Nix crème rinse were found to be statistically similar in the proportion of subjects successfully treated at day 7 (P=0.92).

Outcome	Alpharma	Nix	p-value
Success	48	52	0.92
Failure	3	3	

Ovicidal Activity

The mean change from baseline in hatch rate amongst subjects who received Alpharma crème rinse was –0.013 and for those who received Nix crème rinse was –0.018. These rates were statistically significant (p=0.08).

Re-infestation

This occurred in 3 subjects in the Nix treatment group only and none in the Alpharma group. The difference in re-infestation rate was not statistically significant (p=0.13).

Safety:

Skin and scalp evaluations

All the subjects were evaluated up to 30 hours after administration of treatment and all but 5 subjects were seen for the 7 day evaluation (4 Alpharma, 1 Nix). None of the subjects experienced signs or symptoms or pruritus, erythema, pyoderma, or other skin or scalp condition.

Adverse Events

Four subjects reported five adverse events. These are listed in the table below.

Alpharma	Nix
Rash – 1	Parasitic infection –2
	Furunculosis – 1
	Pharyngitis – 1

All had moderate intensity, no relationship to the study drug, and were ongoing at the end of the study period.

Conclusion:

In this study, the test product, Alpharma 1% Crème Rinse was compared to Nix Crème Rinse in the treatment of lice. The sponsor used an Intent-to-Treat population for bioequivalence evaluation and changed the primary endpoint from treatment success as noted in the protocol to treatment cure. Using their analysis, the two products do not meet equivalence criteria for treatment success but do for treatment cure. When the population is adjusted to reflect an efficacy valid population the results of the analysis are similar and lead to the same conclusion.

Recommendation:

This study should be sent to the relevant new drug division for review. They will need to decide whether they will accept the treatment cure outcome as the primary endpoint. A statistical consult should also be requested.

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