CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-043

PHARMACOLOGY/TOXICOLOGY REVIEW

OTC CONSULT #981807

Review and Evaluation of
Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540, Consult #55)

NDA 21-043

Drug: Rid Mousse (Pyrethrins 0.33%; Piperonyl Butoxide 4.0%)
Category: Pediculicide
Indication: Treatment of Head, Pubic (crab), and Body Lice

Sponsor: SOLTEC RESEARCH PTY LTD
8 Macro Court
Rowville, Victoria 3178
Australia

146 Hillwood Avenue, Suite B
Falls Church, VA 22046
(703) 538-5551

Date Assigned: October 9, 1998
Fileability Date: October 21, 1998
Review Draft Completed: October 15, 1998
Date Review Accepted by Supervisor: October 21, 1998

Formulation and Route of Administration: The product is an aerosolized mouse intended for topical application. It is comprised of a three phase system as follows:

Active Phase:	**Pyrethrum Extract (50%)**	**1.7709 %**
	Piperonyl Butoxide	
	Propylene Glycol	
	Cetearyl Alcohol/PEG-20 Stearate	
	Alcohol SDA 3-C (200 proof)	
		100.00 %
Liquid Phase:	**Purified Water**	
	Quaternium-52	
		100.00 %
Propellant Phase:	**Propellant A-46**	**100.00 %**

The final packaged product is comprised of [redacted] Active Phase, [redacted] Water Phase and [redacted] Propellant Phase. Based on this formulation, the finished product contains [redacted] pyrethrum extract and [redacted] piperonyl butoxide per dose. The actual concentrations of pyrethrum extract and piperonyl butoxide delivered, exclusive of the Propellant Phase, are 0.33 and 4.0 % respectively.

Related Regulations:

1) 21 CFR 358 - Subpart G (358.601 Scope; 358.603 Definitions; 358.610 Pediculicide Active Ingredients; and 358.650 Labeling) - OTC Monograph for Pediculicide Drug Products.

2) 21 CFR 330.11 - NDA Deviations from Applicable Monograph Aerosol Dosage Formulations [dNDAs].

3) 21 CFR 310.545(a)(25)(ii) - Combination of pyrethrum extract and piperonyl butoxide in an aerosol dosage formulation was approved as of June 14, 1994.

BACKGOUND

The final OTC monograph for Pediculicide Drug Products, 21 CFR 358 - Subpart G, defines an over-the-counter pediculicide drug product as a topical drug suitable for treatment of head, pubic (crab), and body lice. The active ingredients consist of combinations of pyrethrum extract (0.17 to 0.33 %) with piperonyl butoxide (2 to 4%) in a nonaerosol dosage formulation.

Pyrethrum extract and piperonyl butoxide, exclusive of the propellant, are present at the maximal allowable concentrations of 0.33 and 4.0 %, respectively. This product differs from the monograph only in that the active ingredients are delivered in an aerosol mousse form. Therefore, pursuant to 21 CFR 330.11, the Sponsors have filed an NDA deviation (dNDA). In compliance with this regulation, only the safety of the deviated formulation need be discussed here.

PHARMACOLOGY/TOXICOLOGY REVIEW

In vitro pediculicidal and ovicidal studies were conducted at [redacted] to evaluate the efficacy of RID Mousse, using the human body lice, *Pediculus humanus humanus* as the surrogate species. For comparison purposes, RID Mousse, a non-aerosolized RID Mousse Concentrate, and two competitive pediculicide shampoos, [redacted] were tested simultaneously.

***In Vitro* Pediculicidal Activity - ICR Study No. 016-0048: An Evaluation to compare the Pediculicidal Activities of Four Candidate Pediculicidal Formulation in the Control of Human Body Lice, PFIZER Protocol No. N0160398004A078; In-Life completion Date 4/22/98.**

Study Design: RID mousse, RID concentrate and two commercially available pediculicide shampoo/conditioners were tested against five replicates of 25 adult human body lice (mixed sexes). Test samples were placed in a glass beaker and stirred for 2 minutes. Lice were then immersed for 10 minutes in the samples, followed by a 1 minute wash and 1 minute rinse with tap water. Lice were transferred to dry petri dishes lined with corduroy cloth and incubated at [redacted] Mortality observations were made at 1 and 24 hours after treatment at 37°C.

Results: All treated samples provided 100 % knockdown (total of moribund and dead lice) 1 hour after treatment. At 24 hours, both the RID Mousse and non-aerosolized concentrate, as well as the [redacted] provided 100 % mortality (moribundity + mortality), while use of the [redacted] provided only approximately 90 % mortality (Table 1). Lice from H_2O treated control plates showed no adverse effects of treatment at 1 hour and 99.8 % survival at 24 hours.

Table 1: Total percent of morbid, dead and recovered lice 24 hours post treatment with various topical pediculicides products.

Treatment	% Moribund*	% Mortality	% Recovery
RID Mousse	22.6	77.4	0.0
RID Concentrate	0.8	99.2	0.0
[redacted]	0.0	100.0	0.0
[redacted]	5.6	84.8	9.6

*Moribund lice were unable to feed and therefore had no chance of survival after 24 hours.

In Vitro Ovicidal Activity - ICR Study No. 016-0049: An Evaluation to compare the Ovicidal Activities of Four Candidate Pediculicidal Formulations in the Control of Human Body Lice (PFIZER Protocol No. N0160398004A079); In-Life completion Date 5/7/98.

Study Design: This study was designed to study the efficacy of the above test products against 30 nits of human body lice. This test utilized a 10 minute immersion of the nits (5 replicates attached to hair shafts) in the test product followed by a 1 minute tap water wash and a 1 minute tap water rinse. The nits were then blotted dry and incubated at [redacted] When all control eggs had hatched (approximately 12 days), replicate test samples were examined for mortality. Eggs failing to hatch represent egg mortality.

Hatched – those eggs from which the nymph has emerged completely. An empty clear egg case with the operculum clearly open.

Unhatched – those eggs that are opaque. The operculum is closed or the nymph is partly emerged.

Results: Treatments with RID Mousse and concentrate and [redacted] resulted in 100 % ovicidal activity, while only approximately 20 % of the nits treated with [redacted] failed to hatch. Table 2 shows the distribution of mortality throughout the three stages of nit development. All products were most effect during the late stages of development.

Table 2: Corrected mean % mortality by stage in lice nits treated for 10 minutes with various topical pediculicides products, and then incubated for up to 12 days.

Treatment	Early	Late	Emergent
H_2O Control	0.1 %	7.3 %	2.3 %
RID Mousse	1.0	98.4	0.1
RID Concentrate	25.0	74.9	0.0
[redacted]	0.1	12.1	7.3
[redacted]	0.3	99.5	0.0

SUMMARY AND DISCUSSION

Efficacy: In the *in vitro* assays performed, RID Mousse performed as well as or better than the concentrate or the two competitive products to which it was compared when looking at the combined effects of its pediculicidal and ovicidal activity on *Pediculus humanus humanus. In vitro* studies with *Pediculus humanus humanus* are generally used as screening studies performed prior to demonstrating efficacy in human clinical trials. In the absence of clinical efficacy trials, the question is whether 1) this is a valid surrogate for head lice, and 2) if *in vitro* studies using a surrogate strain of lice can be used as the only proof of efficacy.

In speaking with a representative [redacted] it appears that *Pediculus humanus humanus* is the only louse currently propagated in the laboratory. It does not have similar resistance profiles as wild type lice and they were unaware of any studies which compared suceptability profiles between this line and wide types (head or body). However, it was stated that after nearly 30 years of propagation, this was not a particularly robust line. From this information, it appears that unless this assay has been found acceptable as the sole proof of efficacy for other drug products covered under the Pediculicide monograph, the Sponsors should be asked to submit evidence that *Pediculus humanus humanus* is a valid surrogate for wild type head lice and that clinical efficacy studies are not needed.

Information which is deemed necessary to utilize the *in vitro* pediculicidal and ovicidal assays to support claims of efficacy and bioequivalence are as follows:

1) The Sponsor should submit a rationale for the use of the *in vitro* assays as a surrogate for clinical trial.

2) The strain of lice used in the *in vitro* study, *Pediculus humanus humanus*, is a body louse perpetuated in the laboratory. As such, it lacks the robust nature of wild type strains and does not appear to be an effective surrogate to evaluate either resistance or sensitivity. The Sponsor should submitted data to justify the use of the body lice strain *Pediculus humanus humanus* as a surrogate for wild type head, pubic and body lice.

3) The surrogate *in vitro* assay does not mimic actual use, e.g., 2 minute stirring prior to application to body lice attached to corduroy, vs direct application to dry hair for the treatment of hair lice. The Sponsor should provide data on the time necessary for the mousse matrix to "break down", releasing the active ingredients, or any 'actual use data' to insure 100 % mortality within the specified 10 minute treatment period allowable in the pediculicide monograph label.

Safety: The safe use of RID Mousse does not appear to present any hazards which are not also associated with the presently marketed shampoos and would not present the safety hazards associated with most aerosols, i.e., inhalation of suspended particles. In addition, the formulation has the added advantage of being applied to dry hair in a foam matrix with reduced risk of accidental inoculation of the eyes.

Labeling: Standard labeling as described in 21 CFR 358.650 appears to be adequate for this product if the *in vitro* surrogate body lice assay is also validated for head and pubic lice.

CONCLUSIONS

From the standpoint of Pharmacology/Toxicology, RID Mousse appears safe, however efficacy and bioequivalence have not been demonstrated with this formulation for the treatment of human head lice.

REQUESTED INFORMATION FROM SPONSOR

1) Please submit a rationale for the use of the *in vitro* assays as a surrogate for clinical trials; or data to justify the use of the body lice strain *Pediculus humanus humanus* as a surrogate for wild type head, pubic and body lice.

2) The strain of lice used in the *in vitro* study, *Pediculus humanus humanus*, is a body louse perpetuated in the laboratory. As such, it lacks the robust nature of wild type strains and does not appear to be an effective surrogate to evaluate either resistance or sensitivity. Please submitted data to justify the use of the body lice strain *Pediculus humanus humanus* as a surrogate for wild type head, pubic and body lice.

3) The surrogate *in vitro* assay does not mimic actual use, e.g., 2 minute stirring prior to application to body lice attached to corduroy, vs direct application to dry hair for the treatment of hair lice. Please provide data that will demonstrate that the mousse matrix "breaks down", releasing the active ingredients (or any 'actual use data') resulting in 100 % mortality within the specified 10 minute treatment period allowable in the pediculicide monograph label.

/S/ 10-21-98

Lynnda Reid, Ph.D. Date
Pharmacologist/Toxicologist

cc:
NDA 21-043
HFD-540
HFD-560
HFD-540/Pharm/Reid
HFD-540/Pharm/Jacobs
HFD-560/DD/Bowen
HFD-560/CSO/Merritt
HFD-560/Katz/
HFD-560/Benson
HFD-560/Kennedy
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