CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-043

MEDICAL REVIEW

OTC Review

NDA#: 21-043
Drug: RID Mousse (pyrethrins 0.33% / piperonyl butoxide 4%)
Sponsor: Soltec (Pfizer)
Purpose: Pediculicide
Date of Submission: August 31, 1998
Date of Review: June 23, 1999

Background

The OTC pediculicide drug product final monograph [Pediculicide Drug Products for Over-the-Counter Human Use; Final Rule, December 14, 1993] allows as active ingredients only the combination of pyrethrum extract (containing a concentration of pyrethrins of 0.17 to 0.33%) with piperonyl butoxide (2 to 4%) in a nonaerosol dosage formulation. The Sponsor has been marketing an aerosol pediculicide product in Australia since 1994 under the trade name BanLice containing the combination of pyrethrum extract and piperonyl butoxide but in a foam aerosol mousse vehicle. The Sponsor has previously met with members of the Division of Dermatologic and Dental Drug Products, the Division of Over-the-Counter Drug Products, and the Office Director to discuss the aerosolized foam mousse formulation. It was agreed that the Sponsor could submit an NDA deviation (dNDA) (refer to 21 CFR 330.11) for the aerosol mousse pediculicide, provided that the concentrations of its active ingredients fell within the range allowed by the monograph. This application would contain Chemistry, Manufacturing and Control information, with safety and efficacy information referenced to the OTC monograph, since the former is the parameter that deviates from the monograph.

This aerosol mousse pediculicide will be marketed under the trade name RID Mousse by Pfizer working with Soltec. Pfizer will be responsible for final testing and release of finished products entering the marketplace. A similar BanLice product has been marketed since 1994 in Australia, where approximately [redacted] units have been sold; however, the active ingredients in BanLice are below the minimum concentration allowed in the US OTC pediculicide monograph as noted in Table 1 below (inactive ingredients being qualitatively the same).

Table 1

	BanLice	RID Mousse	OTC monograph
Pyrethrins	0.168%	0.33%	0.17-0.33%
Piperonyl butoxide	1.68%	4%	2-4%

The Sponsor has decided to reformulate BanLice with the active ingredients at the upper limit of the OTC monograph range and has submitted an application as an NDA deviation. The reformulated product RID Mousse meets the conditions of the pediculicide monograph except that it is an aerosol mousse formulation. The TFM for pediculicides classified the active ingredients pyrethrum extract and piperonyl butoxide *in an*

aerosolized product as Category III for effectiveness and Category I for safety (54 FR 13480 at 13485; April 3, 1989). The TFM stated, in response to comments that aerosolized pediculicides were classified as Category I for safety under the conditions listed in Table 2.

Table 2 Conditions listed in the TFM for Category I safety classification

1. an appropriate applicator is used which facilitates application of the product in close proximity to the affected area
2. less than 2% of the delivered aerosol (by weight) is comprised of particles smaller than 16 microns in diameter
3. the labeling states that the mouth and eyes are closed during application and the facial area is appropriately covered (e.g., with a damp cloth during spraying)
4. the labeling based upon adequate data, states an appropriate time period during which the product can be safely and effectively used before washing off the affected area
5. the directions provide for an initial treatment followed by a second treatment in 7-10 days to kill any nits that may have hatched.

The Sponsor states that the aerosol mousse vehicle is not a true aerosol, that particle size is not an issue, and that the mousse without its propellant is a common emulsion which is subject to the OTC monograph. In response to a previous petition for an aerosol foam product containing pyrethrum extract and piperonyl butoxide (Docket No. 94P-0200), the Agency took the position that "an aerosol foam dosage formulation should not be exempt from the nonaerosol dosage formulation requirement in the final monograph" and that clinical data are required to support effectiveness of the product. However, during Agency discussions with Soltec regarding RID Mousse, the Agency took the position that the monograph was specifically concerned with traditional spray aerosols and that clinical trials are not required prior to approval for marketing of RID Mousse, if the concentrations of the active ingredients fall within the specifications of the OTC monograph. The Agency considered the Sponsor's Australian marketing experience since 1994 with the BanLice product, although at a lower concentration of the active ingredients, in making the determination that a NDA deviation could be filed.

The Agency requested safety and distribution information from BanLice marketing experience in Australia and these data will be reviewed here. The Sponsor states that labeling for the product will be in accordance with the monograph except for added information specific to the mousse formulation.

In vitro studies

The Sponsor has included in the submission *in vitro* data from two studies of the pediculicidal and ovicidal activity of RID Mousse. These studies were reviewed by the pharmacology/toxicology reviewer from the Division of Dermatologic and Dental Drug Products. Study 016-0048 used adult body lice from a laboratory strain of *Pediculus humanus humanus* and compared RID Mousse with three liquid/shampoo formulations of pyrethrum extract and piperonyl butoxide. The study protocol involved a ten minute immersion of 125 adult lice (five replicates of 25) in the product followed by a 1 minute wash and a 1 minute tap water rinse. At 24 hours after treatment, RID Mousse yielded 77.4% mortality and 22.6% moribund lice that were evaluated as unable to feed, and therefore, unable to survive. One of the comparison formulations, a RID liquid concentrate (non-mousse formulation) yielded 100% mortality at 24 hours after treatment. The second of the included studies, 016-0049, compared the same four product formulations on 150 nits (five replicates of 30) after a 10 minute immersion, 1 minute wash and 1 minute tap water rinse. The RID Mousse yielded 1% early mortality, 98.4 % late mortality, and 0.1% emergent mortality, while the RID liquid concentrate yielded 25% early mortality, 74.9 % late mortality, and 0 % emergent mortality (early and late refer to the stage of embryo development attained before death, and emergent means that the embryo developed fully but was not able to leave the nit completely).

The *in vitro* studies showed that RID Mousse was 100% pediculicidal (as measured by combining the percents of dead and moribund lice at 24 hours) and 99% ovicidal (all stages combined). These combined rates were the same as for the RID liquid concentrate and compared favorably to those of the other two competitive shampoo formulations. However, the RID Mousse caused lower 24-hour mortality of adult lice, and it killed nits at a later stage on the average than the RID liquid concentrate, suggesting that the two formulations may differ in pediculicidal and ovicidal activity. The validity of this methodology to extrapolate to human efficacy is not established, because the laboratory strain of *Pediculus humanus humanus* is less robust than wild head or body lice and may not be a realistic surrogate for all lice, and the *in vitro* tests do not simulate actual use as indicated by the pharmacologist/toxicologist reviewer. However, the present dNDA application is not required to include efficacy data but can reference the monograph. In addition, as the biopharmakineticist has noted, there are no established *in vitro* or *in vivo* test protocols for efficacy/bioequivalence of pediculicides.

Adverse Events

The Sponsor submitted a review of 12 Adverse Event (AE) reports for the Australian BanLice formulation of which more than [redacted] units have been sold. These events were recorded in Pfizer's worldwide safety database as part of their post marketing surveillance. There were no reports that could be classified as serious and no reported deaths. Twelve reports involving 25 nonserious adverse reactions were classified and submitted (one event was reclassified by the reviewer as two events upon examination of the data) (see Appendix A, Table 3).

Minimal information was provided on medical history and concomitant medications. One, possibly two, of the events was consistent with an allergic reaction. The first of these, case number 9615441, involved malaise and pharyngitis the day after the first use, an abdominal rash after the second use, and severe urticaria and diarrhea after the third use. This case was evaluated by a physician as an allergic reaction and was treated with prednisone. The other case, number 9715814, developed a rash within 15 minutes of the first use. The dermatologist was unable to identify the etiology. The patient reported that her lice were not eradicated by the BanLice treatment. In addition to these two cases, there were three reports of alopecia, two reports of hair breaking off or being brittle, two cases in one family of hair becoming a lighter color, and four additional reports of application site reactions (itching, redness, pain or irritation). There was one possibly related AE with nausea, paresthesia, and hypesthesia of which we do not know the outcome and which did not abate after 24 hours. In this case the product was applied for 40 minutes (not 10 as directed) and may have caused pyrethrin toxicity. There was one additional case of nausea associated with headache after a second application of BanLice (one week after the first), and two reports of lack of drug effect (including case 9715814 already described). In summary, the number of reported AEs from the Australian database is minimal, and does not appear to present a significant safety concern.

Conclusion and Recommendations

Although the Australian AE reports are supportive of safety, there are differences between the BanLice and RID Mousse formulations. BanLice has a lower concentration of active ingredients than is planned for RID Mousse. In addition, the BanLice label advises a second application only if necessary in 8-10 days, whereas the RID Mousse label will direct a second application in 7-10 days. Nevertheless, the RID Mousse formulation remains within the Category I concentrations of pyrethrum extract and piperonyl butoxide listed in the final monograph for OTC pediculicide drug products.

After evaluating studies of an aerosol spray formulation, the Agency stated in the April 3, 1989 pediculicide TFM that *aerosolized* pediculicides are Category I for safety. However RID Mousse is not a spray aerosol, but a foam aerosol. The chemist states that RID Mousse is a solution emulsified with a propellant and delivers a thick creamy mass about the consistency of shave cream. It is classified as an aerosol because it contains a propellant and is filled into a pressurized container. Testing for airborne particulates is not done on this type of product. The phamacology/toxicology reviewer states that use of RID Mousse does not appear to present any hazards which are not also associated with the presently marketed shampoos.

Factors that weigh in favor of approving the marketing of RID Mousse OTC are the presence of active ingredients in concentrations as listed in the pediculicide monograph and 5 years of OTC marketing experience in Australia of a similar but less concentrated aerosol mousse formulation. The *in vitro* studies showed that the aerosol and nonaerosol formulations have comparable activity against the laboratory strain of body louse.

Label directions should be consistent with the requirements as listed in the final monograph for OTC pediculicide drug products. The label claims cannot include "kills eggs" as this was never proven in a clinical trial. Flammability statements and precautions are required. Directions and warnings pertaining to application of a foam aerosol should also be added.

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ADR's on BanLice since prc aunch in March 1994 to the present time

Case Number	Indica	Age	Sex	Death /Serious	Route of Administr ation	Dose	Adverse Reactions	E. abated after use stopped	Other Meds	PMH	Comments
9615439	head l	8	F	no	topical		hair became lighter color after use; lack of effect	NA	unk	unk	
9615440	head l	unk	F	no	topical		hair became lighter color after use	NA	unk	unk	
9615441	head l	11	F	no	topical	qodX3	urticaria, allergic reaction, malaise, diarrhea, pharyngitis	yes	unk	asthma, previous allergies	Day after 1st use, felt unwell and sore throat; Day of 2nd use, noticed rash on abdomen while showering; On day of 3rd use, rash developed into severe urticaria and pt then developed diarrhea. Tx'd with prednisone. MD felt this was allergic reaction.
9706411	head l	unk	F	no	topical		hair damage (alopecia, application complication)	yes	unk	unk	Hair began to break off about one inch from the scalp. Also used a metal lice comb after applying BanLice
9707428	head l	unk	F	no	topical		alopecia, application site reaction	yes	unk	allergies to many skin products including skin creams and sunscreens	Female treated her children, husband and self w/ BanLice. She had a skin reaction of scalp with some hair loss. Was told her scalp appeared burnt. Was treated w/ topical steroidal prep and antihistamine and problem appears under control.
9710741	head l	unk	F	no	topical		pruritic irritated scalp (application site reaction)		unk	unk	
9713009	pedicu	unk	F	no	topical		headache, nausea after using BanLice a second time a week later		unk	unk	?used 1 package
9715814	head l	55	F	no	topical		rash, lack of drug effect	no	unk	unk	Within 15 minutes of use developed a rash on the back of her neck which has persisted ~4 weeks, and has spread to other parts of her body. Rash appears to migrate, and presents as red bumps. Dermatologist unable to identify etiology.
9803061	head l	unk	F	no	topical		application site pain	yes	unk	unk	mild acid-like burning sensation on hand by mother who is MD and applied product to her child
9803062	head l	5	F	no	topical		application site pain (some redness and tenderness)	yes	unk	unk	patient's mother, an MD, reported daughter experienced mild acid like burning to her scalp and R shoulder whild having product applied. Was treated by rinsing with water and using ice pack. Stated contents smelled foul.
9813130	head l	6	F	no	topical		alopecia, hair disorder, rash		unk	unk	2 days after using according to directions, consumer's 6 year old daughter developed a bald spot 2 inches long, and 1 inch wide at the top of the back of the head. Scalp was red; hair was brittle and snapped off at the root; remainder of the hair dry.
9824634	head l	unk	F	no	topical	left on for 40 minute	nausea, paresthesia, hypesthesia	no	unk	atopic	1 application for 40 minutes. She experienced unusual sensations down her right side of her body, numbness on right face and gums and nausea. The event has not abated after 24 hours.