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N-19435 1 OF 2

MDA 19435

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NDA 19-435/S-001

1988

Mr. Donald A. Knight
Burrroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Knight:

We acknowledge the receipt on January 20, 1988 of your supplemental New Drug Application dated January 14, 1988 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for NIX (permethrin) Creme Rinse 15.

The supplemental application provides for modifications in the synthesis of permethrin, involving primarily an additional distillation of the acid chloride intermediate, to improve its quality.

We have completed our review of this supplemental application and it is approved. Our letter dated March 31, 1986 detailed the conditions relating to the approval of this application.

Sincerely yours,

ARC

Armand R. Casola, Ph.D.
Supervisory Chemist
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA
HFD-520
HFD-520/CSO/Bostwick
HFD-520/ARCasola
HFD-520/HO/Huene
HFD-520/Wayland gm 7/1/88 *LHW 7/1/88*
HFD-520/Gavrilevich
R/D init. by: ARCasola 6/29/88 *ARC 7/8/88*
Approve
1075c

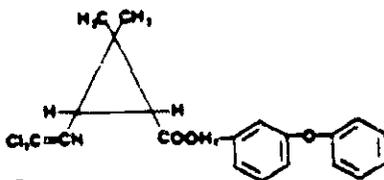


NDA SUPPLEMENT REVIEW

CHEMIST'S REVIEW		1. ORGANIZATION DAIDP	2. NDA NUMBER 19-435
3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE) Burroughs Wellcome Co. 3030 Cornwallis Road Research Triangle Park, NC 27709		4. AF NUMBER	
6. NAME OF DRUG NIX	7. NONPROPRIETARY NAME permethrin	5. SUPPLEMENT(S) NUMBER(S) DATE(S) S-001 1/14/88	
8. SUPPLEMENT(S) PROVIDES FOR: a change in the synthesis of permethrin involving an additional distillation of the acid chloride intermediate to improve its quality.		9. AMENDMENTS AND OTHER (REPORTS, etc) DATES	
10. PHARMACOLOGICAL CATEGORY pediculicide	11. HOW DISPENSED X Rx OTC	12. RELATED IND/NDA/DMF(S)	
13. DOSAGE FORM(S) creme rinse	14. POTENCY(ies) 1%		

15. CHEMICAL NAME AND STRUCTURE

Permethrin, Medical Grade, consists of a mixture of the cis- and trans-isomers of 1-phenoxybenzyl 3-(2,2-dimethyl-3-(2,2-dimethylcyclopropanecarboxylate) in a nominal ratio of 25:75.



16. RECORDS AND REPORTS

CURRENT	
Yes	No
REVIEWED	
Yes	No

17. COMMENTS

Several modifications have been made in the synthesis of NDS by the manufacturer (The Wellcome Foundation, Ltd, Dartford, England). They are not substantive changes, acting only to enhance the purity of the acid chloride intermediate in the already approved synthesis. The specifications of the NDS remain unchanged. Comparative data between lots of intermediate produced by both old and new processes show a purer product resulting from the modifications.

Stability data on a lot of drug product using new process NDS show a satisfactory product. The stability studies will continue according to the approved protocol.

18. CONCLUSIONS AND RECOMMENDATIONS:

The supplement is for changes being effected. From the manufacturing and controls standpoint it may be approved.

cc: ORIG NDA
HFD-520 HFD-520/CSO
HFD-520/MO HFD-520/Wayland: gm 7/1/88
R/D initialed by: ARCasola 6/29/88

ACC 7/8/88

19. REVIEWER		
NAME Lola G. Wayland	SIGNATURE <i>Lola G. Wayland</i>	DATE COMPLETED 6-28-88
DISTRIBUTION	ORIGINAL JACKET	REVIEWER DIVISION FILE

NDA 19-435/S-002

SEP

Mr. Donald A. Knight
Associate Director, Regulatory Affairs
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Knight:

We acknowledge the receipt on March 9, 1988 of your supplemental New Drug Application dated March 9, 1988 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for NIX (permethrin) Creme Rinse 1%

The supplemental application provides for broadening the limits for preservatives in the drug product from _____, and tightening the impurity limits in the new drug substance.

We have completed the review of this supplemental application and it is approved. Our letter of March 31, 1986 detailed the conditions concerning the approval of this application.

Sincerely yours,

ARC

Armand R. Casola, Ph.D.
Supervisory Chemist
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: cc: Orig NDA
HFD-520
HFD-520/CSO/Bostwick
HFD-520/ARCasola
HFD-520/MO/Huene
HFD-520/Wayland gm 8/30/88 *AW 8/30/88*
R/D init. by: ARCasola 8/29/88 *ARC 8/31/88*
Approve
35c

NDA SUPPLEMENT REVIEW

AUG 31

CHEMIST'S REVIEW	1. ORGANIZATION DAIDP	2. NDA NUMBER 19-435
3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE) Burroughs Wellcome Co. 3030 Cornwallis Road Research Triangle Park, NC 27709	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER(S) DATE(S) S-002 3/09/88
6. NAME OF DRUG NIX	7. NONPROPRIETARY NAME permethrin	

8. SUPPLEMENT(S) PROVIDES FOR:
revising the NDS specifications relating to impurities and broadening the limits for preservatives in the drug product from

9. AMENDMENTS AND OTHER (REPORTS, etc) DATES

10. PHARMACOLOGICAL CATEGORY pediculicide	11. HOW DISPENSED X Rx OTC	12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM(s) topical creme rinse	14. POTENCY(ies) 1%	

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS	
	CURRENT	
	Yes	No
	REVIEWED	
	Yes	No

17. COMMENTS
To support the broadening of the 3 preservatives' limits, data are presented demonstrating preservative effectiveness to microbial challenge at levels representing 25, 50, 75, and 100% of labeled preservative strength. Assay values of all 3 preservatives at each level are presented. Since the data show effectiveness at a level as low as 25% of label, broadening of the specifications from 1% is reasonable and still offers a large margin of safety.

COMMENTS CONT. ON NEXT PAGE

18. CONCLUSIONS AND RECOMMENDATIONS:
The supplement may be approved.

cc: cc: Orig NDA
HFD-520
HFD-520/CSO/Bostwick
HFD-520/ARCasola
HFD-520/MO/Huene
HFD-520/Wayland gm 8/30/88
R/D init. by: ARCasola 8/29/88 *ARC 8/31/88*

19.	REVIEWER		
NAME	SIGNATURE	DATE COMPLETED	
Lola G. Wayland	<i>Lola G. Wayland</i>	8-26-88	
DISTRIBUTION	ORIGINAL JACKET	REVIEWER	DIVISION FILE

Bostwick

NDA 19-435

MAR 31 1985

George M. Lyon, Jr., M.D.
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Dear Dr. Lyon:

Reference is made to your New Drug Application dated February 28, 1985, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nix (permethrin) Creme Rinse, 1%.

Reference is also made to your additional communications dated May 28, 1985, July 1 and 11, 1985, August 14, 1985, September 20, 1985, and March 26, 1986.

We have completed our review of this application including the submitted draft labeling and the application is approved. However, prior to marketing, the following changes must be made in the labeling:

1. The first sentence of the CLINICAL PHARMACOLOGY section should read as follows:

Permethrin is a synthetic pyrethroid, active against lice, ticks, mites, and fleas.

2. The second sentence of the second paragraph in the CLINICAL PHARMACOLOGY section should be revised as follows:

Although the amount of permethrin absorbed after a single application of the 1% Creme Rinse has not been determined precisely, preliminary data suggest it is less than 2% of the amount applied.

3. Because residual drug on hair was measured only up to ten days in the single application study, the last sentence of the second paragraph in the CLINICAL PHARMACOLOGY section should read as follows:

Residual persistence of Nix is detectable on the hair for at least 10 days following a single application.

4. The word "excellent" should be deleted from the first sentence of the "Pediculicidal/Ovicidal Activities" subsection of the CLINICAL PHARMACOLOGY section. In addition, the second sentence of this subsection should be revised to include the words "demonstrated at 14 days" after "head lice."

10. The trade name Nix should be inserted where (Trade Name) was used in the draft labeling.

The labeling should be revised exactly as we have requested and twelve copies of the final printed version of the revised labeling must be submitted to FDA.

Because the data submitted do not allow a precise determination to be made of the amount of permethrin absorbed after a single application of the 1% Creme Rinse, we request that you conduct a post-marketing study to provide that information.

In addition, please submit in duplicate all advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products and a second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Also, when a market package is available, please send one to the Division of Anti-Infective Drug Products.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

for Elaine C. Esber

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

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We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

for James Buttal

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

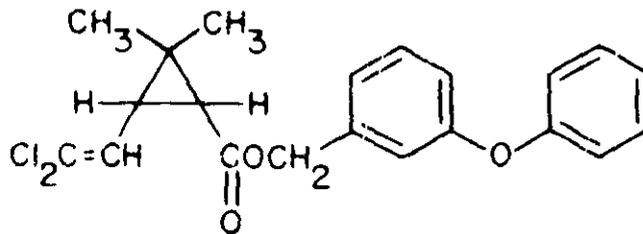
1989

**NIX™
(PERMETHRIN) 1%
Creme Rinse**



DESCRIPTION: Nix™ (Permethrin) 1% Creme Rinse is a topical pediculicide and ovide for the treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). The product is a creme rinse, each gram containing Permethrin 10 mg (1%). Inactive ingredients are: stearylalkonium chloride, hydrolyzed animal protein, cetyl alcohol, polyoxyethylene 10 cetyl ether, hydroxyethylcellulose, balsam canadensis, fragrance, citric acid, propylene glycol and FD&C Yellow No. 6. Also contains isopropyl alcohol 200 mg (20%) and added as preservatives: methylparaben 2 mg (0.2%), propylparaben 0.8 mg (0.08%) and imidazolidinyl urea 2 mg (0.2%).

Permethrin is a mixture of the *cis* and *trans* isomers of the synthetic pyrethroid (+/-)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (*cis/trans* 75/25). It is a yellow to light orange-brown low melting solid or viscous liquid. The molecular weight is 391.29 and the structural formula is



CLINICAL PHARMACOLOGY: Permethrin is a synthetic pyrethroid, active against lice, ticks, mites, and fleas. It acts on the nerve cell membrane to disrupt the sodium channel current by which the polarization of the membrane is regulated. Delayed repolarization and paralysis of the pests are the consequences of this disturbance.

Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine. Although the amount of permethrin absorbed after a single application of the 1% Creme Rinse has not been determined precisely, preliminary data suggest it is less than 2% of the amount applied. Residual persistence of Nix is detectable on the hair for at least 10 days following a single application.

PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovidical activity against *Pediculus humanus var. capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovidical activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovidical activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative

NIX™ (PERMETHRIN) 1% CREME RINSE

data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies.

Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effect. Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching, 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort, and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

OVERDOSAGE: No instance of accidental ingestion of Nix has been reported. If ingested, gastric lavage and general supportive measures should be employed.

DOSE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt/wt) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g (NDC-0081-0780-81).

Store at 15°-25°C (59°-77°F).

MEDICAL OFFICER'S REVIEW OF NDA 19-435
ORIGINAL SUBMISSION

250
Please return to
D.C. Bodurich,
Rm. 12B-45

Date: October 2, 1985

SPONSOR: Burroughs Wellcome Co.
Research Triangle Park, NC

DRUG: Permethrin creme rinse 1%

CLINICAL INDICATION: Pediculosis capitis (head lice)

FORMULATION:

*Permethrin 1.0%

Isopropyl alcohol

Hair conditioner 18N195-M

*present as 25:75 cis:trans permethrin

The hair conditioner vehicle is produced by Kolmar Labs; reference is made to their master file. The ingredients of the vehicle are as follows.

Stearalkonium chloride	Citric acid
	Polyoxyethylene 10 cetyl ether
	Cetyl alcohol
Imidazolidinyl urea	Balsam Canada
Hydrolyzed animal protein	FD&C yellow #6
Hydroxyethylcellulose	
Propylene glycol	

DATE OF SUBMISSION: February 28, 1985, amended 9/26/85

CONTROLS REVIEW: The application has several deficiencies relating to controls and stability, of which the sponsor has been apprised.

PHARMACOLOGY REVIEW: Dr. Gamil Debbas has recommended revision of the pharmacology section of the labeling, but did not have objections to approval of the NDA.

HISTORY AND RATIONALE FOR USE: Permethrin is chemically and pharmacologically related to the naturally occurring pyrethrins, insecticides which are derived from the chrysanthemum. It is one of a large number of synthetic analogs of pyrethrin known as pyrethroids, which have been developed to increase the insecticidal potency and overcome the photochemical instability of pyrethrin. Introduced in 1973, permethrin is stated to be the first relatively stable pyrethroid with an insecticidal potency 50 to 100 times greater than the pyrethrins.

The insecticidal mechanism of the pyrethrins and the pyrethroids appear to be the same. They are neurotoxins which act primarily on physicochemical processes rather than on biochemical ones. It has been demonstrated in both vertebrate and invertebrate systems that the intact molecule is required for neurotoxic activity. The very low mammalian toxicity of the pyrethrins, especially as compared with other classes of insecticides, is partly attributed to rapid esterase hydrolysis of the molecule by the ubiquitous plasma and tissue esterase activity in mammals, including man. The natural pyrethrins also rapidly undergo photodecomposition to inactive products in the presence of oxygen and ultraviolet light.

The sponsor feels that permethrin creme rinse has significant advantages over the other formulations used for the treatment of head lice in the US, which contain either lindane (gamma-benzene hexachloride), malathion, or natural pyrethrins, because of the relative safety, greater effectiveness, and the convenience of a single application.

In vitro studies

Preliminary studies on solutions of 0.01-1.0% permethrin showed effective pediculicidal and ovicidal activity of the 0.5% and 1.0% concentrations against *Pediculus humanus var. capitis*. The effect of various organic solvents was studied, and it was found that permethrin in isopropanol had potent ovicidal activity.

Professor David Taplin of the University of Miami performed studies on a number of formulations containing 1% or 5% permethrin and varying amounts of organic solvents in conventional shampoo and hair conditioner (creme rinse) formulae. A vehicle control for each formulation was included, as were a water control, a dry control, and Kwell shampoo. The shampoo formulations were found to be unsuitable, as they were unstable with the organic solvents, and without the solvents the permethrin did not dissolve.

The methodology for Prof. Taplin's study was adapted from the 1975 World Health Organization document entitled "Instructions for Determining the Susceptibility or Resistance of Body Lice and Head Lice to Insecticides". For the determination of adult pediculicidal activity, at least ten adult lice from infested subjects were exposed to cloth impregnated with the test formulations. The lice were observed for activity at 10, 30, 60, and 120 minutes, and at 4 and 24 hours. To determine ovicidal activity, a minimum of 20 hairs with attached viable nits were dipped for five minutes in each test formulation. They were then rinsed with clear water, dried, and incubated for 14 days.

Pertinent results were as follows. Pediculicidal activity is expressed as the percent of adult lice killed at each observation time. Ovicidal activity is expressed as the percent of unhatched nits observed at 14 days.

NDA 19-435

- 3 -

<u>Formulation</u>	<u>Pediculicidal activity</u>			
	<u>Percent Adult Lice Killed</u>			
	<u>10 min</u>	<u>30 min</u>	<u>60 min</u>	<u>120 min</u>

Conclusions were that the creme rinse base had negligible pediculicidal and ovicidal activity. When permethrin was added, it did not dissolve and had only modest activity. With permethrin solubilized in isopropanol, however, the formulation had excellent pediculicidal and ovicidal activity.

Clinical safety studies

The clinical safety studies on the 1% Permethrin creme rinse consisted of a sensitization study and topical and systemic tolerance and absorption studies after a single application and after multiple applications. Phototoxicity and photosensitization studies were done on a 5% permethrin cream. The studies were conducted by James Leyden, M.D., and Kays Kaidbey, M.D., of the Department of Dermatology, University of Pennsylvania. Additional information on safety includes adverse reactions which occurred in the clinical effectiveness studies, studies performed in England on other permethrin formulations, and a literature review of clinical trials of permethrin.

1) Sensitization: A maximization test was performed on 37 subjects. After pre-treatment of a skin site with 2% sodium lauryl sulfate, application of the 1% Permethrin creme rinse was made under an occlusive patch for 48 hours. This procedure was repeated for a total of five applications to the same skin site over a period of 10 days. After pre-treatment of a new skin site with 10% sodium lauryl sulfate for one hour, the test product was applied under occlusion for 48 hours. The site was then similarly treated for an additional 24 hours. Twelve of the subjects were also simultaneously treated with Kwell Lotion and RID.

Results were that no reactions occurred with any of the test products.

2) Phototoxicity and photosensitization: In the phototoxicity study, applications of 5 ul/cm² of a 5% permethrin cream were made to delineated skin sites of 10 subjects, followed by occlusion for 6 hours. The sites were then exposed to long wave ultraviolet and visible light at a dose of 20-25 joules/cm². One control site was similarly treated but not irradiated, and a second control site was treated with the cream vehicle and irradiated. No reactions were found.

The photosensitization study was performed on 25 subjects. In the induction phase, 10 ul/cm² of a 5% permethrin cream was applied with occlusion for 24 hours. After removal of the patch, the site was immediately exposed to 3 MED of ultraviolet light. This procedure was repeated to the same skin site for a total of six exposures over a period of three weeks. The challenge was conducted ten days after the last exposure. Application of 5 ul/cm² of the test material was made to a new skin site, followed by occlusion for 24 hours. The site was then exposed to 4 joules/cm² of long wave ultraviolet. A similarly treated but unirradiated site served as a control. The sites were examined 72 hours later for erythema and edema. Results were that there were no reactions during either the induction or challenge phase.

The sponsor states that although these studies were performed with a formulation which differed from that of the Permethrin creme rinse, it is felt that these results are directly applicable to the Permethrin creme rinse, since the ingredients in the rinse other than the permethrin are known to be free of phototoxic or photoallergenic potential.

3) Topical and systemic tolerance and absorption after a single application:

This study was performed on 10 subjects. Following a shampoo with Prell and a clear water rinse, the hair was dried, and Permethrin creme rinse 1% was applied in a sufficient amount to saturate the hair and scalp (25-50 cc). The rinse was left on the hair for 10 minutes and then rinsed out with clear water. The subjects did not shampoo for 24 hours after application of the creme rinse, but resumed their normal hair grooming practices thereafter.

The subjects were evaluated at 24 hours and at 7 days after application for subjective complaints and objective abnormalities of the scalp and adjacent skin. The following clinical laboratory tests were done prior to application, and at 24 hours and 7-10 days after application: CBC with differential, Hgb, SGOT, SGPT, LDH, AP, bilirubin, total protein, albumin, BUN, creatinine, uric acid, glucose, cholesterol, triglycerides, electrolytes, and urinalysis. Hair samples for measurement of permethrin levels were obtained at 24 hours and at 7-10 days after application. Urine and plasma were examined for permethrin and/or metabolites for 7-10 days after treatment.

Results were that there were no abnormalities of the scalp or skin, and no subjective complaints were reported. There were no consistent laboratory abnormalities found, and none were considered to be drug-related.

The detection limit for drug in the plasma was 5 ng/ml. Of 70 plasma specimens assayed for drug, only one had detectable levels of permethrin. The concentrations were 20.5 and 6.3 ng/ml of cis- and trans-permethrin, respectively. This was a 2 hour post-treatment specimen, the subject did not subsequently show detectable plasma levels or metabolites in the urine, and it was thought that inadvertent contamination might have occurred. In the urine assay the detection limit for metabolites was 2.5 ng/ml. Measurable levels of metabolite, in a range of 22.4 - 47.2 ng/ml, were found in 9 of 59 urine samples, with no detectable levels in the 7-10 day samples. All of the subjects had measurable levels in the hair throughout the 10 day period, with the levels at 7-10 days approximately 10-50% of those at the 24 hour period.

4) Topical and systemic tolerance and absorption after multiple applications:

This study was performed on 10 subjects, using the same procedure as in the single application study. Following a shampoo with Prell and a clear water rinse, the hair was dried, and Permethrin creme rinse 1% was applied in a sufficient amount to saturate the hair and the scalp (25-50cc). The rinse was left on the hair for 10 minutes and then rinsed out with clear water. This was repeated weekly for 8 weeks. The subjects were not permitted to shampoo for 24 hours after each application, but were otherwise permitted to continue their usual hair grooming practices. The subjects were evaluated at one and two weeks after the last application.

Prior to each application and at the followup visits the subjects were evaluated for subjective complaints and objective abnormalities of the scalp and adjacent skin. Hemograms and clinical chemistries as in the single

application study were done prior to the first, fourth and eighth applications. Hair samples for permethrin levels, and urine and plasma for permethrin and/or metabolites were obtained during the course of the study and in the followup period.

There were no abnormalities of the scalp or skin, no subjective complaints, and no significant laboratory abnormalities. Detectable plasma levels of permethrin, in a range of 5 - 20 ng/ml, were found in two samples from week 6 and three samples from week 8. Detectable urine levels of 2.5-25 ng/ml of metabolites were found in one sample at week 8. Results of the hair sample assays were similar to those in the single application study, with no accumulation of drug found, and a decrease in levels of approximately one-third at two weeks after the last application.

The sponsor was asked by this reviewer to estimate the percentage of applied drug that was absorbed in these studies, and the sponsor has provided this information in the submission of 9/26/85. Because there was only one plasma sample with quantifiable levels of permethrin, and urine samples had levels of metabolites mostly below quantifiable levels, the sponsor based the estimation upon assumptions and extrapolations from studies on other topical permethrin formulations and oral permethrin. Their estimation for the amount of permethrin absorbed when 50cc of the 1% permethrin rinse is applied to the scalp is 1.6% of the applied dose, or 7.8 mg permethrin.

5) Adverse reactions in clinical effectiveness studies: The clinical effectiveness studies consisted of a single investigator study in which 29 patients were treated with Permethrin creme rinse, and a multicenter study in which 260 patients were treated with the rinse. There were no adverse reactions reported in the first study. In the second study the nature and frequency of adverse reactions with permethrin were comparable to that in the control group treated with Kwell, and consisted of symptoms such as burning/stinging, tingling, numbness, or scalp pain in 3%, mild scalp irritation in a few patients, and a transient rash in one patient. These are described further under the review of the clinical effectiveness studies.

6) Studies on other permethrin formulations: Clinical tolerance and absorption studies were performed on two other formulations of permethrin, a lotion and an aerosol, by the Wellcome Foundation Ltd. in England. The lotion contained odorless paraffin. The permethrin was present as 25% cis and 75% trans forms, as in the creme rinse formulation.

An absorption study on the lotion was performed on 10 subjects. Application was made in a sufficient volume to wet the hair, which then dried naturally. The hair was washed 24 hours later. Urine and hair assays for permethrin and/or metabolites were performed for 14 days after application. Three subjects developed a mild, patchy erythema which faded in a few days. Based on the urine assays, it was estimated that from 0.6 - 2.5% of the applied dose was absorbed and excreted. The concentration of permethrin remaining on the hair 14 days after application ranged from 2% to 23% of the amount measured immediately after application.

An absorption study on the aerosol was performed on 10 subjects, using a procedure similar to that in the lotion study. One subject developed a mild patchy erythema which was still present at day 7, and one developed a mild transient seborrheic dermatitis. Based on the urine assays, it was estimated that 0.9% of the applied dose was absorbed and excreted.

A preliminary study on the local tolerance and effectiveness of the lotion and aerosol was performed by Professor David Taplin in Panama on 60 patients with head lice. The patients were treated with either the active lotion or placebo lotion for 30 minutes or two hours, or with the active or placebo aerosol for two hours or four hours. Only 1 of 20 patients treated with the active lotion, and 1 of 20 treated with the active aerosol had live lice present at 14 days after application, as compared with 17 of 20 placebo treated patients. No adverse reactions were reported.

A multicenter comparative clinical trial was performed in England on 385 children with head lice. Of these, 195 were treated with 1% permethrin lotion, 144 with Prioderm (0.5% malathion), and 46 with Derbac (0.5% malathion). The permethrin lotion was applied for two hours and the malathion products for twelve hours. The scalps were examined for irritation and live lice at 24 hours, 7 days, and 6 weeks after treatment. Infestation after treatment was found in 3 patients (1.5%) treated with permethrin, in 5 patients (3.5%) on Prioderm, and in 1 Patient (2.2%) on Derbac. Adverse reactions were reported in about 7% of each treatment group, these were similar in each group and consisted of eye or scalp burning or stinging, and 1 - 2 cases each of hair loss, headache, nausea, and GI upset.

An additional multicenter clinical trial was performed in England on 568 children with head lice. Of these, 298 were treated with the permethrin 0.67% aerosol, 176 with Prioderm, 67 with Derbac, and 27 with Carylderm (0.5% carbaryl). The permethrin aerosol was applied for two hours and the other products for twelve hours. The scalps were examined for irritation and live lice at 24 hours, 7 days, and 6 weeks after treatment. Infestation after treatment was found in 12 patients (4%) on permethrin, 4 (2.3%) on Prioderm, 2 (3%) on Derbac, and in 4 (14.8%) on Carylderm. Similar adverse reactions were reported in 9% on permethrin, 6% on Prioderm, and in 44% on Carylderm, these consisted of eye or scalp burning or stinging, red sore patches on the scalp or neck, and one case each of headache, faintness, facial erythema, and epistaxis.

7) Literature review: There are no published studies on the use of permethrin for the treatment of head lice; however, it has been used for body lice and scabies, and as a protective by clothing impregnation or spray.

One report was on the use of 1% permethrin talc (25:75 cis:trans) to treat body lice infestations in 300 inhabitants of an Egyptian village. The powder was blown through the sleeves and collar and around the neckband of each patient's clothing, in an amount of 30-50 gm/person. The patients were examined at intervals for one month. The infestation rate prior to treatment was greater than 60%. On day 8 after treatment the infestation rate was 2%, as compared to an infestation rate of 68% in a control population. No adverse reactions were reported.

A further study in three similarly infested Egyptian villages compared treatment with 50 gm of either 2.5 gm/kg or 5 gm/kg permethrin powders to untreated controls. Administration was in the same manner as in the previous study. The patients were examined at 2 weeks and three months after treatment. At two weeks 99% and 100% of the patients were free of lice in the groups treated with the 2.5 gm/kg and 5 gm/kg powders, respectively, while the untreated group remained the same. No adverse reactions were reported.

A comparative trial of permethrin and lindane was performed in patients with scabies in Rhodesia. Administration was a single whole body application of 2% lindane in liquid paraffin to 134 patients and 1% permethrin in liquid paraffin to 95 patients. Followup examination at 2-3 weeks on 32 patients treated with lindane and 38 treated with permethrin showed a cure rate of about 60% in both groups. No adverse reactions were reported.

Studies have been performed by the U.S. Army and the U. S. Department of Agriculture on the use of permethrin-impregnated clothing (0.125 mg/cm^2) as a protectant against chigger mites, for which effectiveness was reported with no adverse reactions. There have also been several other reports of the effectiveness of permethrin impregnated clothing and aerosol sprays against various arthropods; no adverse reactions were reported in these studies.

Effectiveness studies

The clinical studies consisted of a single center study performed in Panama and a multicenter domestic study.

Study I. This study was performed by the following co-investigators:

Professor David Taplin
Department of Dermatology
University of Miami School of Medicine
Miami, FL

Pedro Castellero, M.D.
Ministry of Health
Panama City, Panama

The conduct of the study was as follows.

- 1) Study design: This was a double blind parallel group comparison of 1% Permethrin creme rinse with placebo (the vehicle) in patients infested with *Pediculus humanus var. capitis*, with random assignment of patients to the two treatment groups. A third concomitant but non-blinded arm of the study was a group treated with Kwell shampoo (1% lindane).
- 2) Patient selection: The patients were primarily children of an indigenous Indian population, in whom the diagnosis was established by the identification of live adult lice or nymphs. The presence of nits only was not acceptable.
- 3) Patient exclusions: Patients were excluded if they had used any other pediculicide within one week prior to the study, or if they were taking any anti-infective medication.
- 4) Treatment regimen: After a shampoo with Prell, the creme rinse formulations were applied in sufficient quantity, from 10 to 50 cc, to saturate the hair and scalp, and remained for 10 minutes on the scalp before being rinsed out with clear water. The Kwell shampoo was applied to dry hair for 4 minutes, then lathered and rinsed out. Nits were not combed out of the hair after treatment. The patients did not shampoo their hair for 24 hours after treatment, and did not use any other hair grooming aid, medicated shampoo, or pediculicide during the course of the study.
- 5) Effectiveness parameters: The patients were observed for the presence or absence of live adult lice or nymphs at 1, 2, 4, 6, and 24 hours, and 7 and 14 days after treatment. Ten hairs with apparently viable nits were also taken for incubation immediately after treatment.
- 6) Tolerance evaluation: At each followup visit, an assessment of the presence or absence of the following symptoms and signs was made: pruritus, burning/stinging, pain, numbness, tingling, edema, erythema, or rash.

Results were as follows.

- 1) Demographic characteristics: Ninety-three patients were enrolled in the study, of which 29 were treated with 1% Permethrin creme rinse, 34 were treated with placebo, and 30 were treated with Kwell. It is stated that there were no differences between treatment groups in regard to age, sex, and hair characteristics such as texture, length, and curliness. Almost all patients were considered to have heavy louse infestations prior to treatment, defined as the presence of more than five adult lice or nymphs.

2) Pediculicidal and ovicidal effect: The number and percentage of patients that were free of adult lice or nymphs at the 7 and 14 day evaluations were as follows.

	<u>Pediculicidal rates</u>		
	<u>7 days</u>	<u>14 days</u>	<u># pts</u>
Permethrin	29 (100%)	28 (97%)	29
Placebo	3 (9%)	2 (6%)	34
Kwell	20 (67%)	13 (43%)	30

It was felt that the frequency of Kwell treatment failures was higher than would be expected in the U.S., probably due to a high frequency of resistance to organochlorides among insects in general in Central America.

The viable nits obtained prior to treatment showed a hatch rate of over 90% in all three groups. The mean percentages of nits obtained immediately after treatment that subsequently hatched on incubation were as follows:

<u>Mean hatch rates</u>	
Permethrin	30%
Placebo	86%
Kwell	55%

The differences between groups in pediculicidal and ovicidal activity was stated to be highly statistically significant.

In only three of the 29 patients treated with permethrin did none of the post-treatment nits hatch on incubation. It was therefore concluded that the clinical effectiveness at 14 days was due to the residual permethrin on the hair shaft, and that the residual pediculicidal activity may be more important than the ovicidal activity.

3) Tolerance: No subjective complaints or objective adverse effects were reported.

Study II. This study was performed by the following investigators.

Joan DiNapoli, R.N., Ph.D.
Consultation and Research, Inc.
Durham, NC

Joseph Orthoefer, DVM, MPH
Winnebago Department of Public Health
Rockford, IL

Lawrence Parish, M.D.
Paddington Testing Co., Inc.
Philadelphia, PA

Doris Wagner, R.N., M.S.
Marion County Health Department
Indianapolis, IN

Steven Englander, M.D., MPH
Department of Health Sciences
Phoenix, AZ

Kathie Brandenburg, R.N., MS
City of Nashua Community Health Department
Nashua, NH

Amos Deinard, M.D.
University of Minnesota Hospitals
Minneapolis, MN

The conduct of the study was as follows.

1) Study design: This was a single blind (investigator blind) parallel group comparison of 1% Permethrin creme rinse and Kwell shampoo in the treatment of head louse infestations. Persons who were the initial patient in a family were designated 'index cases', and were randomly assigned to one of the treatment groups. Whenever possible, other family members were evaluated, and if afflicted, were treated with the same medication as the index case.

2) Patient selection: The patients were primarily children, in whom the diagnosis was established by the identification of live adult lice or nymphs. The presence of nits only was not acceptable.

3) Patient exclusions: Patients were excluded if they had any other abnormal scalp or hair condition, or if any other pediculicide had been used within one week of the the study.

4) Treatment regimen: After a shampoo with Prell, a sufficient quantity of Permethrin rinse (25-50 cc) was applied to saturate the hair and scalp, and remained for 10 minutes before being rinsed out with clear water. In the alternate group Kwell shampoo was applied to the dry hair in sufficient quantity to saturate the hair (25-50 cc), remained for 4 minutes, and was then lathered and rinsed out, this was in accord with the manufacturer's directions. Nits were not combed from the hair after treatment. The patients did not shampoo their hair for 24 hours after treatment, and did not use any other hair grooming aid, medicated shampoo, or pediculicide during the study.

5) Effectiveness parameters: Followup evaluations were done by a staff member other than the one who had administered treatment at 24 hours, 7 days (range 5-10 days), and 14 days (range 12-16 days). Each patient was examined for five minutes for the presence or absence of live adult lice or nymphs, apparently with an illuminated macromagnification technique.

6) Tolerance evaluation: At 30-60 minutes after treatment and at each subsequent return visit an assessment for the following symptoms and signs was made: rash, erythema, edema, pruritus, burning/stinging, numbness, tingling, or scalp discomfort.

In evaluating the results, the sponsor found that the patients were not properly randomized in one study, that of Dr. Orthoefer, and that the blind may have been broken when the medication was distributed, in an effort to treat all the children at a particular school with Permethrin. For this reason the sponsor analysed the results with and without the Orthoefer study.

Because of the high rates of effectiveness shown with Permethrin in the pooled results, this reviewer did not feel that there was a need for review of the individual studies. The results were as follows.

Pooled results

1) Demographic characteristics: A total of 577 patients were enrolled in the study, of which 331 were index cases, i.e., randomly assigned to treatment. Of these, 512 patients, including 292 index cases, were fully evaluable for effectiveness at 14 days.

The demographic characteristics were as follows.

	<u>Permethrin</u>	<u>Kwell</u>
<u>No. of pts</u>	290	273
<u>Age</u>		
1-5	49 (17%)	53 (20%)
6-10	156 (54%)	136 (50%)
11-15	39 (13%)	38 (14%)
16-20	2 (1%)	6 (2%)
> 20	43 (15%)	39 (14%)

	<u>Permethrin</u>	<u>Kwell</u>
<u>Sex</u>		
Female	175 (60%)	178 (65%)
Male	115 (40%)	95 (35%)
<u>Race</u>		
White	256 (88%)	229 (84%)
Black	0 (0%)	4 (1%)
Hispanic	16 (6%)	18 (6%)
Other	18 (5%)	22 (10%)
<u>Hair texture</u>		
Fine	82 (28%)	70 (26%)
Average	171 (62%)	176 (64%)
Coarse	29 (10%)	27 (10%)
<u>Hair curliness</u>		
Straight	228 (79%)	226 (83%)
Curly	61 (21%)	45 (16%)
Kinked	1 (0%)	2 (1%)

The baseline infestation rates were as follows.

	<u>Baseline infestation</u>		<u># pts</u>
	<u>1-5 lice</u>	<u>> 5 lice</u>	
<u>All patients</u>			
Permethrin	216 (83%)	44 (17%)	260
Kwell	195 (77%)	57 (23%)	252
<u>Index cases</u>			
Permethrin	122 (82%)	27 (18%)	149
Kwell	104 (73%)	39 (27%)	143

(The above table is from the statistical report, and is at variance with the summary report; the latter appears to be in error.)

It was found that 13 patients inadvertently had been treated twice, and one had been treated three times, for reinfestations. Only the first entry of these patients was included in the analysis of results. (Nine of the 13 were originally treated with Kwell and four with Permethrin, all had been free of lice at the 14 day evaluation). The sponsor was asked by this reviewer to provide

a further explanation of the dropouts than was given in the original submission, and this information has been provided in the submission of 9/26/85. The summation of reasons for exclusion from the efficacy analyses, for both index cases and for all patients, is as follows.

	<u>Index pts</u>	<u>All pts</u>
No. patients entered	331	577
No. patients excluded		
Second entry	9	13
Third entry	1	1
Protocol violations	4	7
Dropouts, reasons unrelated	7	11
Dropouts, reasons unknown	18	33
Total pts excluded	39	65

Of the 33 dropouts for unknown reasons, 13 (8 index) were in the Kwell group, and 20 (10 index) were in the Permethrin group.

The number of evaluable patients per investigator was as follows.

	<u># pts</u>
DiNapoli	156
Orthoefer	94
Parish	4
Wagner	97
Englander	82
Brandenburg	24
Deinard	55

Investigator DiNapoli conducted studies at three centers, so that nine separate centers were involved in the study.

2) Pediculicidal effect: The number and percentage of patients that were free of live adult lice and nymphs at the day 7 and 14 evaluations were as follows.

	<u>Pediculicidal rates</u>	
	<u>Kwell</u>	<u>Permethrin</u>
<u>All patients</u>		
Day 7	228/248 (92%)	259/260 (99%)
Day 14	215/252 (85%)	257/260 (99%)
<u>Index cases</u>		
Day 7	133/143 (93%)	148/149 (99%)
Day 14	121/143 (85%)	148/149 (99%)

The most meaningful comparison was felt to be that of the results at 14 days with the index cases; statistical analysis showed Permethrin to be significantly superior to Kwell in this parameter ($p < 0.001$).

Results at the individual centers for the index cases were as follows. At two of the centers all patients were cured, and at all seven of the other centers the proportion cured was greater in the Permethrin group. The differences were statistically significant in two of the centers ($p < 0.005$).

Of the 13 patients treated for reinfestations, 11 were treated with Permethrin and 2 with Kwell, one treatment failure occurred in a Permethrin patient who had previously been successfully treated with Kwell.

Tabulation of the data with omission of the Orthoefer study, which had not been properly randomized and blinded, was as follows.

	<u>Pediculicidal rates</u>	
	<u>Kwell</u>	<u>Permethrin</u>
<u>All patients</u>		
Day 7	199/217 (92%)	193/194 (99%)
Day 14	188/222 (85%)	193/196 (98%)
<u>Index cases</u>		
Day 7	105/113 (93%)	106/107 (99%)
Day 14	95/114 (83%)	108/109 (99%)

Statistical analysis of the results for the index cases at 14 days showed Permethrin to be significantly superior to Kwell ($p < 0.001$).

3) Adverse reactions: All 577 patients entered into the study had at least one evaluation following treatment, and thus all provided information on safety. The occurrence of the symptoms and signs which were assessed at each visit was divided into three categories, as follows.

- a) Pruritus alone which appeared or was aggravated after treatment was regarded as primarily disease-related. This was reported in 17 (6%) of the Permethrin group and in 13 (5%) of the Kwell group.
- b) Symptoms other than or in addition to pruritus (burning/stinging, tingling, numbness, or scalp pain) which appeared or were aggravated after treatment were regarded as possibly drug-related; these were reported in 10 (3%) of the Permethrin group and in 10 (4%) of the Kwell group.
- c) Objective signs (erythema, edema, rash) which appeared or were aggravated after treatment were regarded as probably drug-related; these were reported in 6 (2%) of the Permethrin group and in 8 (3%) of the Kwell group.

Nearly all of the above adverse experiences were mild and transient. One case of burning/stinging with Permethrin and one rash with Kwell were reported as moderate in severity, and one case of tingling with Kwell was reported as severe. The six category c adverse reactions in the Permethrin group were as follows: a mild papular rash in 1 patient which had resolved by 7 days, mild scalp redness in 3 patients, and mild redness and edema in 2 patients. The eight category c reactions in the Kwell group were as follows: mild erythema in 4, mild rash in 3, and a moderate rash in 1 patient.

Adverse experiences apart from the protocol assessments which were possibly related to treatment were reported in three of the Permethrin group and in two of the Kwell group. These were transient headache in 1, and scabs of the scalp presumed due to excoriation in 2 of the Permethrin group, and a rash and an open lesion of the scalp in 1 patient and hives in another patient in the Kwell group.

The incidence of reported adverse reactions varied considerably among the different centers. In three of the seven centers no adverse reactions were reported. The largest number, 31 reactions, and proportion, 29% of the treated group, were reported by the center at Indianapolis. The incidence of reactions in the remaining centers varied between these numbers.

In a separate ongoing study on prophylaxis, one patient developed a severe rash of the neck and shoulders after application of the Permethrin rinse vehicle, and later had a more severe reaction when the patient subsequently used the Prell shampoo that she had obtained in the study. The sponsor feels that patients should be advised to use a shampoo product with which they are familiar in conjunction with the use of Permethrin rinse.

Labeling review: The product is for prescription use. The trade name has not yet been determined. The directions for use are for a single application of an amount sufficient to saturate the hair and scalp, to remain for 10 minutes before being rinsed with water.

The package insert is felt to be satisfactory.

Summary and evaluation

It is felt that the product is safe and effective for the proposed clinical use.

Safety: The clinical safety studies consisted of a sensitization study and topical and systemic tolerance and absorption studies after single and multiple applications. No sensitization was found. In the systemic absorption studies, no adverse cutaneous reactions or laboratory abnormalities were found after single application or after eight weekly applications to groups of 10 subjects each, with applications made according to the proposed clinical use. It was estimated that about 1.6% of the applied dose of permethrin was absorbed.

In the clinical effectiveness studies, done on about 600 patients, the nature and frequency of adverse reactions with Permethrin were comparable to those in the control group treated with Kwell.

Effectiveness: The effectiveness studies consisted of a double blind comparison with the vehicle in a single center study, and a single blind (investigator blind) comparison with Kwell in a multicenter study.

The first study was conducted on 63 patients. The parameters for effectiveness were observation for adult lice or nymphs for 14 days after treatment, and the incubation of ova taken immediately after treatment to determine viability. Permethrin was significantly superior to the vehicle in both pediculicidal and ovicidal rates. The pediculicidal rate was very high, 97% at 14 days, but the ovicidal rate, 70% of the sampled nits, was less satisfactory. (A third arm of this study was a non-blinded comparison with Kwell; although results with Permethrin were much superior to those with Kwell, these were not considered to be valid because of a probable resistance to Kwell in this Central American country).

The second study was performed by seven investigators on 512 evaluable patients at nine centers. This included 292 'index cases'; an index case was the initial patient in a family, who was randomized to one of the treatment groups. The remaining patients were other afflicted family members who were treated with the same medication as the index case. The parameter for effectiveness was observation for adult lice or nymphs at 7 and 14 days after treatment; the ovicidal effect was not determined.

In the pooled results, the pediculicidal rate at 14 days with Permethrin rinse was very high, 99%, and was significantly superior to that with Kwell. The effectiveness was apparent at each of the nine centers; all patients were cured in two centers, and the cure rate was greater in the Permethrin group at each of the other seven centers, with results at two centers showing a statistically significant difference.

The incubation period for head lice ova is generally considered to be 6 to 8 days. To confirm this, we consulted Prof. David Taplin of the University of Miami, a recognized authority, who stated that all ova would have hatched during the 14 day period.

The results of the two studies indicate that Permethrin rinse has a greater pediculicidal than ovicidal effect, which is to be expected, as ova are more difficult to treat. In addition to a direct ovicidal effect, the effectiveness on ova is apparently due to residual amounts of the drug in the scalp which are lethal to emerging nymphs. Previous clinical studies confirmed that detectable amounts of drug remained on the hair for ten days after application.

Recommendations: It is recommended that the application be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFN-815
HFN-815/DCBostwick HFN-340
HFN-815/PHuene
4481b

ET 11/19/85
C.C.E.
10/21/85

NDA 19-435

June 17, 1987

Clinical Review of Final Printed Labeling

Date of Submission: April 25, 1986

Sponsor: Burroughs Wellcome Co.
Research Triangle Park, N.C.

Drug: Nix (permethrin) Creme Rinse

Reason for Submission: In our approval letter of March 31, 1986, a number of labeling changes were requested prior to initiation of marketing of the drug. This submission consists of FPL which implements the requested changes.

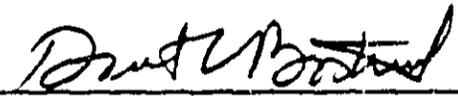
Material Reviewed

We have compared the FDA requests to the submitted labeling and find that the revised labeling contains the requested changes and is satisfactory.

A call was made to Burroughs Wellcome management to determine the status of the absorption study which was requested in the approval letter. (A determination was to be made of the amount of permethrin absorbed after a single application of the drug). We were informed that the study has been completed and the results will be submitted "within a month."

Finally, we have received a memorandum from the Division of OTC Drug Evaluation which recommends that "hypersensitivity to ragweed" be added to the Contraindications for this drug (memo dated March 16, 1987, signed by Dr. Gilbertson). The OTC monograph for pediculicides proposes the following statement under "Warnings": "Use with caution on persons allergic to ragweed." We do not feel that there are sufficient data available to justify ragweed allergy as a contraindication to use of Nix. No adverse reactions of this type was noted in clinical trials or during subsequent marketing. The labeling for this product is adequate as submitted April 25, 1986.

Recommendation: None at this time.


David C. Bostwick


P. A. Huene, M.D.

cc"
Orig NDA
HFN-815, HFN-210
HFN-340 *LC* *ET 7/1/87*
HFN-815/PAHuene
HFN-815/DBostwick:js/6/18/87
2500m *C.C.E.*
7/1/87

Done B.

Division of Anti-Infective
Drug Products
Chemist's Review #2
Date Completed: 7/19/85

A.1. ~~NYK~~ 19-435

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

2. Product Names:

Non-proprietary: permethrin, cis: trans (25:75)

3. Dosage Form & Route of Administration: Rx, Cream rinse for hair

4. Pharmacological Category and/or Principal Indication: Topical pediculicide and oviceide

5. Structural Formula and Chemical Name(s):

B. 1. Initial Submission: 2/28/85

2. Amendments: 7-11-85; labeling 8-15-85

C. Remarks:

Most deficiencies noted in Chemist's Review #1 have been satisfactorily addressed. Questions relating to labeling have now been resolved. (21 CFR 201.10(2)).

Method validations have not been completed.

D. Conclusions and/or Recommendations:

Method validation results have not been received. No action is indicated until they are received.

Lola G. Wayland
Lola G. Wayland

cc: Orig. NDA
HFN-815
R/D Init. by: ARCAsola
HFN-815/MO
0073c

HFN-815/CSO
ARCAsola 8/29/85

HFN-815/Wayland: gm 8/29/85

ARC 8/30/85

Division of Anti-Infective
Drug Products
Chemist's Review #1
Date Completed: 5/10/85

A.1. NDA 19-435

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

2. Product Names:

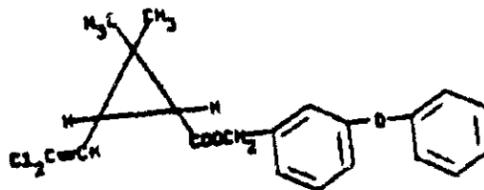
Non-proprietary: permethrin, cis: trans(25:75)

3. Dosage Form & Route of Administration: Rx, Creme rinse for hair

4. Pharmacological Category and/or Principal Indication: Topical pediculicide and oviceide.

5. Structural Formula and Chemical Name(s):

Permethrin 25/75 consists of a mixture of the cis- and trans-isomers of 3-phenoxybenzyl-2', 2'-dimethyl-3'-(2', 2'-dichloroethyl) cyclopropane-1'-carboxylate in a nominal ratio of 25:75.



B. 1. Initial Submission: 2/28/85

C. Remarks:

Several deficiencies exist relating to laboratory controls and stability which have been communicated to the applicant's regulatory advisor (see meeting report). Methods validations have been requested of DDC and Atlanta District.

D. Conclusions and/or Recommendations:

The application is deficient with regard to manufacturing and controls under 505(b)(4) of th Act. The applicant has agreed to respond in a timely manner to the meeting report (5-9-85), and telecon (5-16-85) (attached) describing the deficiencies, so a non-approval letter should not issue at this time.

Lola G. Wayland
Lola G. Wayland

cc: Orig. NDA
HFN-815
R/D Init. by: ARCasola 5/17/85
HFN-815/MO
4043b

HFN-815/CSO

HFN-815/Wayland: gm 5/20/85

ARC 5/23/85

Division of Anti-Infective
Drug Products
Chemist's Review #3
Date Completed: 9/23/85

A.1. NDA 19-435

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

2. Product Names:

Non-proprietary: permethrin, cis: trans (25:75)

3. Dosage Form & Route of Administration: Rx, Cream rinse for hair

4. Pharmacological Category and/or Principal Indication: Topical
pediculicide and ovice

5. Structural Formula and Chemical Name(s):

B. 1. Initial Submission: 2/28/85

2. Amendments: 7-11-85; 8-15-85

C. Remarks:

Method validation results have been received from Atlanta District (sent 8-1-85; rec'd by me 9-19-85) and the Division of Drug Chemistry. Minor difficulties were experienced with the NDS, partly because not all degradation products could be obtained. Results of testing the drug product are satisfactory and are consistent with results reported by the manufacturer. The assay method for permethrin in the creme rinse is suitable to serve as a regulatory method.

D. Conclusions and/or Recommendations:

Method validation results are satisfactory. The NDA submission is now approvable from the manufacturing and controls standpoint.

Lola G. Wayland
Lola G. Wayland

cc: Orig. NDA

HFN-815

HFN-815/CSO

HFN-815/Wayland: gm 9/24/85

R/D Init. by: ARCAsola 9/24/85

ARC 9/30/85

HFN-815/MO

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REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-435 (Original Submission, dated 2/28/85)

Date Received: 3/5/85

Date Review Completed: 7/22/85

Applicant: Burroughs Wellcome Co., Research Triangle Park, NC

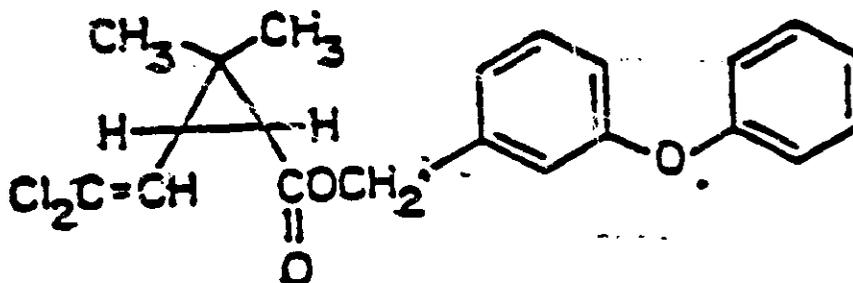
Drug: Permethrin Creme Rinse, 1%

Alternate Name: 21Z73

Category: Pediculicide [Eradication of Pediculus humanus capitis (head lice)]

Related Submissions: IND : (Permethrin Creme Rinse, 1%);
IND : [Permethrin 5% Dermal Cream (scabicide)]

Chemistry:



Permethrin is a mixture of the cis and trans isomers of the active synthetic pyrethroid, (+,-)-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. The permethrin produced by The Wellcome Foundation, Ltd., Dartford, England, used in the manufacture of PERMETHRIN 1% CREME RINSE, consists of 25% cis and 75% trans forms of the molecule."

Composition:

PERMETHRIN CREME RINSE, 1%

Each Gram Contains 10 mg Permethrin

- | | <u>g per 100 g</u> |
|--|--------------------|
| * Permethrin, Medical Grade
(includes 5 percent excess) | |
| Isopropyl Alcohol USP
(includes 1 percent excess) | |
| ** Hair Conditioner 18N195-1M | |
- * The weight of permethrin is to be calculated from the potency factor supplied by Quality Assurance. The weight of Hair Conditioner 18N195-1M is adjusted accordingly.
- ** Hair Conditioner 18N201M may be used as an alternate.
- Both 18N195-1M and 18N201M contain the same components and at the same concentrations, except for the dyes as follows:
- Conditioner 18N195-1M contains FD&C Yellow No. 6, whereas conditioner 18N201M contains FD&C Yellow No. 5. Components are listed in Kolmar DMF

Clinical Indications: Permethrin Creme Rinse 1% is proposed for single-application treatment of infestation with Pediculus humanus var. capitis (head lice) and its eggs. Retreatment may be required for less than 1% of the patients. The labeling recommends that the drug be applied for 10 min. after the hair is shampooed & dried, then allowed to remain on for 10 min. before being rinsed off with water.

Previous Pharmacology Reviews: IND' both dated 3/31/83; reviews of both dated 5/2/83.

Original Submissions of

List of Preclinical Studies

Labs Performing Studies:

[A] = Wellcome Research Laboratories, Research Triangle Park, NC
 [R] = T.P.S. Inc, Mt. Vernon, Indiana
 [C] = Wellcome Research Laboratories (Berkhamsted), U.K.
 [D] = " " " " (Beckenham), " "

* = Lab indicated under "Title".
 # = Foreign Studies

<u>Lab</u>	<u>Ref.</u>	<u>Document #</u>	<u>Title</u>	<u>Volume</u>	<u>Page</u>
[A]	48	TPZZ/82/0024	Everitt, B.J. (1982). The general pharmacology of BW 21273 <u>Pharmacology - Metabolism</u>	1.3	105
[A]	52	TYHK/83/0003	Allsup, T.L. & Hubbell, J.P. (1983). The percutaneous absorption of permethrin following application of dermal formulations to male rats		134
*	53		Snodgrass, H.L. & Nelson, D.C. Dermal penetration & distribution of ¹⁴ C-labeled permethrin isomers (Study # 75-51-0351-83) *U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD		181
[B]	57	TTEP/82/0130	Acute Oral Toxicity Study of 1% Permethrin Creme Rinse in the Rat	1.4	1
[B]	58	TTEP/82/0127	Acute Dermal Toxicity Study of 1% Permethrin Creme Rinse in the Rabbit		22
[B]	59	TTEP/82/0128	Acute Eye Irritation Test of 1% Permethrin Creme Rinse in the Rabbit		46
[B]	60	TTEP/82/0129	Acute Skin Irritation Study of 1% Permethrin Creme Rinse in the Rabbit		77
[B]	61	TTEP/82/0126	Sensitization Study of 1% Permethrin Creme Rinse in the Guinea Pig		108
# [C]	62	HEFG 75-4	21273 (25/75) Effect of Different Solvents on the Rat Oral Toxicity		150

<u>Lab</u>	<u>Ref.</u>	<u>Document #</u>	<u>Title</u>	<u>Volume</u>	<u>Page</u>
# [C]	63	HEFG 75-8	21Z73 (25/75) Acute Toxicity Studies by Various Routes of Administration in the Rat, Mouse & Chick		159
# [C]	64	HEFG 77-7	21Z73 - Dermal Toxicity in the Male Rat		175
# [C]	65	HEFG 77-5	21Z73 - Dermal Toxicity in the Female Rat		180
# [C]	66	HEFG 74-6	Ocular Irritancy of 21Z73 in Rabbits		183
# [C]	67	HEFG 74-3	Guinea Pig Sensitization Study with 21Z73 Using the "Maximization" Test Method		186
# [C]	68	HEFG 74-10	Ten-Day Cumulative Oral Toxicity with 21Z73 in Rats		190
# [C]	69	HEFG 74-9	Ten-Day Cumulative Oral Toxicity with 21Z73 in Mice		208
# [C] [D]	70	HEFG 76-1	21Z73, Rat Oral 90-Day Study		215
# [C]	71	HEFG 78-14	Permethrin Oral Administration to Dogs for Six Months	1.5	1
# [D]	72	BPAT 74/19	Fetal Toxicity Study of BW 21Z73 (NRDC 143) in the Rabbit		89
# [D]	73	BPAT 74/10	Fetal Toxicity Study of 21Z73 (NRDC 143) in the Rat		111
# [D]	74	BPAT 74/12	Fetal Toxicity Study of 21Z73 (NRDC 143) in the Mouse		136
# [D]	75	BPAT 79/3	Multigeneration Reproduction Study of 21Z73 (Permethrin) in the Rat		160
[A]	76	TTEP/77/G001	Mutagenicity of BW 21Z73 in L5178 Y/TK ⁺ - Mouse Lymphoma Cells With and Without Exogenous Metabolic Activation		318

<u>Lab</u>	<u>Ref.</u>	<u>Document #</u>	<u>Title</u>	<u>Volume</u>	<u>Page</u>
# [B]	77	HEFG 75-10	21Z73, Dominant Lethal Study in male Mice		335
[B]	78	HEFG 77-C3	Preliminary Investigation of the Neurological Effects in Rats Offered Diets Containing NRDC 143		345
# *	79	HEFG 80-33	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for 104 Weeks *Life Science Research, Stock, Essex, England	1.6	7
# [C]	80	HEFG 81-C044	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks; Addendum to Final Report (HEFG 80-33)	1.9	1
# [C]	81	HEFG 81-C045	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks; Summary Tables of Tissues Examined & Occurrence of Neoplasms; Addendum to Final Report (HEFG 80-33)	1.12	356
# [C]	82	HEFG 81-54	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks; Justification of Exact Number of Tissues Investigated; Addendum to Final Report (HEFG 80-33)		363
# [C]	83	HEFG 80-29	Carcinogenicity Study in Mice with Permethrin (BW 21Z73)	1.13	1
# [C]	84	HEFG 81-C049	Potential Toxicity & Oncogenicity in Dietary Administration to Mice; Addendum to Final Report (HEFG 80-29)	1.15	1
[A]	85	TTDR/81/0030	Additional Historical Data on Incidence of Mouse Pulmonary Lung Adenoma, and Statistical Analysis of the Incidence of Lung Tumor in Female Mice Treated with Permethrin	1.19	424
*	85A		Permethrin. Assessment of Chronic & Oncogenic Effects: A Summary *Tox. Branch, Hazard Eval. Div., Office of Pesticide Programs, EPA (See my review of Report by EPA.)		441

Review of Preclinical Data

The bulk of the preclinical data has been previously reviewed; see "Previous Pharm. Reviews", p.2. Also the reader is referred to Vols. 1.20 & 1.21 of the NDA for a clinical/preclinical bibliography (50 references) from the published literature dealing with the chemistry (structure, activity, biochemical, etc.), pharmacology & toxicology of pyrethrum insecticides & related products (organophosphates, carbamates, etc.).

Preclinical data not previously reviewed are: Ref. Nos. 53, 85 & 85A of the "List of Preclinical Studies."

Reference No. 53:

Dermal Penetration & Distribution of ¹⁴C-labeled Permethrin Isomers in Rabbits & Dogs: The summary report provided by the U.S. Army is adequate and is quoted below:

"a. Purpose. The insecticide permethrin has been proposed as an impregnant in military fatigue uniforms. Formulations contain varying cis-trans isomer mixtures of the chemical. The potential for skin penetration and bodily distribution of individual isomers and a 50/50 mixture was assessed in dogs and rabbits using the radiolabeled chemicals.

b. Essential Findings/Conclusions. Absorption of topically applied permethrin isomers as measured in excreta through 7 or 14 days registered 30 percent in rabbits and 10 percent in dogs. Urinary excretion was the primary elimination pathway accounting for nearly 75 percent of radioactivity appearing in excreta, usually within the first 24 hours. Radiocarbon recovered in feces was consistently higher (2.5 X) following cis permethrin application than for trans. Absorption/elimination kinetics for the cis-trans mixture generally fell between values observed for the individual isomers. No affinity for tissue binding of permethrin moieties was observed in either animal model. Based on the current and earlier tests, absorption of permethrin in man should be less than 8 percent of the applied dose. The projected bioavailability to man from permethrin impregnated fabric (0.125 mg/cm²) should be less than 0.026 mg/kg/day.

c. Recommendations. It is recommended that permethrin be approved for further testing as a clothing or fabric impregnant at concentrations to 0.125 mg/cm² and that the trans isomer significantly predominate in commercial formulations."

Reference No. 85:

Additional Historical Data on Incidence of Mouse Pulmonary Lung Adenoma: Historical control data concerning mouse pulmonary lung adenoma was submitted in response to a critique by EPA. This comprised the incidence in controls from 11 carcinogenicity bioassays. After statistical analysis, the applicant reconfirmed his initial conclusion re: the B.W. mouse study (discussed below).

Table 1

B.W. Mouse Study

Incidence of Lung Tumors in F Mice (CFLP) Treated with Permethrin

<u>Dose Tested</u> <u>mg/kg/day</u>	<u>No. of Lung TBA/No. Examined</u>	<u>Percent Incidence</u>
--	-------------------------------------	--------------------------

*Lung tumor-bearing animals

The table below gives the incidence of lung tumors in untreated female CFLP mice from 11 studies, in which the number of lung TBA is known and documented.

Table 2

<u>Study</u>	<u>No. of TBA/No. Examined</u>	<u>Percent Incidence</u>
--------------	--------------------------------	--------------------------

The applicant pointed out that the control value (3.1%) in the B.W. mouse study was quite low compared to the historical values (range of 12.5-30%) and that the mean % of lung TBA in historical controls (19.2%) is about equal to that of the HD treated group (20.6%). Furthermore, statistical analysis showed no significant findings and it was concluded that permethrin was not oncogenic in mice in the B.W. study.

Reference No. 85APermethrin. Assessment of Chronic & Oncogenic Effects:

Introduction: The applicant submitted 7 chronic oncogenicity feeding studies to EPA in support of requests to register food and other uses of permethrin. The following comprises a summary of the EPA report.

Table 3

List of Studies Submitted to EPA

<u>Study</u>	<u>Animals (No/Sex/Group)</u>	<u>Duration (Weeks)</u>	<u>Dosage Levels (Nominal ppm)</u>
A. <u>Mouse:</u>			
1. ICI	70	98	0, 250, 1000, 2500
2. PMC-I	75	104	0, 20, 500, 4000
3. PMC-II	75 M F	104	0, 20, 500, 2000 0, 20, 2500, 5000
* * 4. B-W	100 75	92	0 10, 50, 250*
B. <u>Rat:</u>			
1. ICI	60	104	0, 500, 1000, 2500
2. PMC	60	104	0, 20, 100, 500
* * 3. B-W	60	104	0, 10, 50, 250*

Note: Test material was 40:60 cis:trans isomer in all studies except the B.W. studies (25:75).

*mg/kg/day M = males; F = females

(a) **#4 (mouse) = Ref. 83 - HEFG 80-29; #3. (rat) = Ref. 79 - HEFG 80-33. Both were previously reviewed.

(b) The remaining (3 mouse & 2 rat) studies were not submitted in this NDA nor in the parent IND's; the reason for this omission was not accounted for by the applicant.

(c) Since EPA had to integrate all the data to arrive at a final conclusion, references 83 & 79 will also be described below with the other studies (as reviewed by EPA).

Labs Performing Studies: To be designated as in the above EPA Table.

Mouse:

- | | |
|-----------|--|
| 1. ICI | Central Toxicology Laboratory, ICI |
| 2. FMC-I* | Not disclosed or reviewed (see below). |
| 3. FMC-II | Bio/Dynamics, Inc. |
| 4. B-W | Applicant |

Rat:

- | | |
|----------|---|
| 1. ICI | Central Toxicology Laboratory, ICI |
| 2. FMC** | Bio/Dynamics, Inc. (Very limited in usefulness; see below.) |
| 3. B-W | Applicant |

The following is a slightly edited (summarized) version of EPA's review:

* The FMC-I mouse study was flawed by dose level changes in the MD & HD gps and by an animal identification problem. For these reasons, the study was disqualified by EPA.

** The FMC Rat study was judged to be of very limited usefulness with regard to evaluation of lung tissues for tumors. This resulted from a failure to treat lungs from control & test animals in a comparable manner during the preparation of these tissues for microscopic exam.

The remaining 5 studies were judged to be adequate in evaluating the oncogenic effects of Permethrin. Four of these, the exception being the FMC-II Mouse study, were also found to be useful in evaluating the chronic toxicity of the compound.

Abbreviations to be used: PT = permethrin; inc = increase; dec = decrease;
SS = statistically significant

Mouse Studies

1. ICI Mouse Study

Strain & # Animals: Alderly Park mice; 70/sex

Dosage, Route & Duration: 0, 250, 1000, 2500 ppm in the diet for 98 wks
(sacrificed at 26, 52 & 98 wks)

Results: Relevant non-oncogenic effects observed during the study were: inc'd mortality; inc'd liver enzyme (aminopyrine-N-demethylase) & liver wts; eosinophilia of hepatocytes in both M & F at 2500 ppm. Liver changes observed in this study were considered to be related in large measure to the induction of liver microsomal enzyme activity. Minimal liver changes were also observed at 1000 ppm, but not at 250 ppm.

Table 4

Type	Males (ppm)				Females (ppm)			
	0	250	1000	2500	0	250	1000	2500
Adenoma	11/70 (15.7)	6/70 (8.6)	13/70 (18.6)	17/70 (24.3)	11/70 (15.7)	8/70 (11.4)	10/70 (14.3)	15/70 (21.4)
Adenocarcinoma & Adenoma	0	0	0	0	0	1	1	1
Incidence								

Slight inc in lung adenomas in M showed a trend (SS), but pairwise comparison for both sexes did not reach SS. Mean time for tumor development did not suggest a shortening of the latency period by PT.

Conclusions: EPA was not certain that lung neoplasia in this study was drug-related. However, since lung adenomas were encountered in 2 other studies (FMC-II Mouse & B-W Mouse), EPA was cautious about disregarding the effect.

2. FMC-I Mouse Study: Not reviewed by EPA.

3. FMC-II Mouse Study

Strain & # Animals: Charles River CD-1 mice; 75/group

Route & Duration: in the diet; 104 wks

Dosages: 0, 20, 500 & 2000 ppm to M; 0, 20, 2500 & 5000 to F

Relevant Non-oncogenic Effects: Inc'd mortality in M at 2000 ppm; inc'd liver wts in F at 2500 & 5000 ppm; inc'd lung wts in F at 5000 ppm; Histopathologically, "focal areas of alveolar cell proliferation" (inc'd nos. of lung cells) was observed with dose-related incidence in PT-treated F. Multifocal hepatocytomegaly (inc'd liver cell vol.) was observed with inc'd frequency in both sexes at the HD levels and to a lesser extent in the other treated gps. Necrosis of the liver did not follow a dose-related pattern. Hepatocytomegaly was thought to be probably related to enzyme induction (as suggested by the other mouse studies) rather than being a precursor of necrosis (i.e., PT toxicity).

Oncogenic Effects:

a) Lung: There was an inc'd incidence of bronchioalveolar adenomas (two separate pathology reports) in F, but not in M, compared to controls (Gp 1), as follows:

Group	I	20.0%
	II (LD)	31.6%
	III (MD)	46.7%
	IV (HD)	58.7%

Furthermore, the number of F mice with alveolar cell adenomas, alveolar cell carcinomas & adenomas and/or carcinomas, demonstrated a sig. dose response.

Various methods of statistical analysis led to the following conclusion by EPA: "Administration of dosage levels of 2500 ppm & 5000 ppm of PT to F mice in this study resulted in a sig. dose-related inc'd incidence of alveolar cell neoplasms (adenoma and/or carcinoma). For alveolar cell carcinomas (alone), the data are somewhat less convincing at the dosage level of 2500 ppm, but there is nevertheless clear evidence of a sig. dose-related inc in alveolar cell carcinomas, particularly at 5000 ppm. PT apparently enhanced the normally expected spontaneous lung tumor incidences in the F, only, in this study."

Note: According to EPA, the total data base did not suggest a dec in latency by PT for induction of tumors.

b) Liver: The incidence of M & F with liver neoplasms (hepatomas & hepatocellular carcinomas) was as follows:

	M (%)	F (%)
Group I	30.1	8.1
II	39.7	9.2
III	48.6	32.9
IV	36.2	40.0

The test for homogeneity of the distribution of liver neoplasms in M was marginally sig. at $p = 0.0740$ (one sided test). In F, there was a SS time-adjusted dose-related trend (Peto's Prevalence Method) with $p \sim 5.5 \times 10^{-10}$ for liver adenoma and/or carcinoma. However, the inc in hepatomas, and not hepatocellular carcinomas, accounted for the inc'd incidence in F. The incidence of hepatocellular carcinoma was not dose-related. There was no indication of a dec'd latency period for liver tumors.

An EPA/FDA joint audit of this study and laboratories conducting /analyzing the results of this study showed it to be useful in determining oncogenic, but not chronic, toxicity effects.

4. B.W. Mouse Study

Strain & # Animals: CFLP mice; 100/sex in control gp, 75/sex in test gps

Dose, Route & Duration: 0 (C), 10 (LD), 50 (MD), 250 (HD) mg/kg/day in the diet for 92 weeks

Relevant Non-oncogenic Effects: Inc'd liver wts in M & inc'd kidney wts in F at the HD. Histologically, M & F of the HD gp showed an inc'd incidence of cuboidal/columnar metaplasia of the alveolar epithelium of

the lung (C = 0% for M & F vs. 4.1% in HD-M & 6.8% in HD-F). "Although controversial, this lesion is considered by some pathologists to be a precursor of lung neoplasms in mice."

Oncogenic Effects: There was a dose-related trend in F (but not M) for adenomatous tumors in the lungs, as follows:

F	%
C	3.1
LD	7.0
MD	9.5
HD	20.3

The incidence was, however, still within historical control range (see EPA report, pp. 25-26).

The occurrence of 3 adenocarcinomas in the lungs of 219 PT-treated F in this study was not indicative in the opinion of EPA to be drug-related. EPA concluded that "the inc'd incidence of lung tumors [adenomas] in F mice observed in this study, together with the other supportive evidence observed in this study, to be highly suggestive of a possible oncogenic effect in lungs of F - particularly when considered in relation to the results of the other two oncogenic studies in mice."

Rat Studies

1. ICI Rat Study: The EPA summary (slightly edited) states the following:

Doses of 0 (C), 500 (LD), 1000 (MD) & 2500 (HD) ppm of PT were administered in the diet to Wistar rats (60/sex/group) for 104 weeks; 11 or 12 rats/sex in each dosage group were sacrificed at 52 wks, the remainder at 105 wks. Relevant non-oncogenic effects were: mortality inc'd in M & dec'd in F at the HD; liver wts inc'd in M & F at the MD & HD and in M only at the LD; liver enzyme (aminopyrine-N-demethylase) activity inc'd in M & F at the MD & HD; hepatocyte vacuolization or hypertrophy in M & F at the MD & HD; kidney wts inc'd in all treated M; pituitary wts inc'd in M at the MD & HD. Body tremors were also observed in M & F during the first 3 wks of the study at the HD.

Conclusion: PT was considered to be non-tumorigenic in this study.

2. FMC Rat Study: PT was administered in the diet to Long-Evans rats (60/sex/group) for 104 weeks at dosage levels of 0, 20, 100 & 500 ppm; 10 M & 8 F from the 100 ppm group were killed at 52 wks. The remaining animals were killed at 104 wks.

Relevant Non-oncogenic Effects: Inc'd liver wts for M at 100 & 500 ppm.

Oncogenic Effects: There was an inc'd incidence of adenomas & adenocarcinomas in the lungs of M rats in this study. However, this study was judged by EPA to be of very limited usefulness with regard to evaluation of lung tumors because of serious flaws in histological methodology (for details, see pp. 15-16 of that report).

NDA 19-435

EPA concluded the following: "Evidence suggests the possibility of an oncogenic effect occurring in the lungs of treated M rats in this study. Sufficient uncertainty regarding the validity of the incidence figures, however, precludes making a scientifically supportable evaluation of the results."

3. B.W. Rat Study: The EPA summary report (slightly edited) states the following:

PT was administered in the diet to Wistar rats (60/sex/gp) for 104 weeks at dosage levels of 0 (C), 10 (LD), 50 (MD) & 250 (HD) mg/kg/day. Relevant non-oncogenic effects observed at the HD were: inc'd mortality in M; inc'd liver wts in M; hepatocyte hypertrophy in M & F; focal disturbances in growth pattern of thyroid follicular cells in M & F. The microscopic liver & thyroid changes were also observed in M & F at the MD.

None of the tumor types observed in this study were considered related to or attributable to the ingestion of PT.

Non-oncogenic NOEL (no effect level) For Mouse Studies

EPA indicated that some of the liver changes noted in all 3 mouse studies were associated with liver microsomal induction (slight inc in liver wts & aminopyrine-N-demethylase activity) and were therefore not considered to be a toxicological manifestation of PT. However, other liver histopathological effects that could be of toxicological significance were used to determine the NOEL (inc in liver wt, multifocal hepatocytomegaly, hepatocytic pigmentation & eosinophilia of hepatocytes).

EPA concluded the following: "...that liver effects were present in the ICI Mouse Study at 1000 ppm (150 mg/kg/day) and higher, and in the B-W Mouse study at 250 mg/kg/day....liver effects were not present in these studies at levels of 250 ppm (37.5 mg/kg/day) & 50 mg/kg/day. The unusual pattern of distribution of multifocal hepatocytomegaly & necrosis of the liver cells in the FMC-II Mouse study (i.e. in control & treated groups) is very difficult to interpret. These effects could be attributable to the general animal health problems observed in this study or, in the case of hepatocytomegaly, to the ingestion of PT. The Toxicology Branch takes the position that the hepatocytomegaly observed in the 2000, 2500 & 5000 ppm (300, 375 & 750 mg/kg/day) level mice is treatment-related. The weight of evidence favors the 50 mg/kg/day level in the B-W Mouse Study as an appropriate mouse non-oncogenic NOEL."

Non-Oncogenic NOEL for Rat Studies

EPA concluded the following: "As with mice, a consistent finding in all 3 rat studies was liver changes known to be associated with induction of the microsomal enzyme system. This induction phenomenon, for reasons already presented, was again not considered to be an adverse or toxicological effect of concern. The other toxic effects [discussed previously] were used to determine a non-oncogenic NOEL for the rat studies. The NOEL for each study was judged to be: FMC Rat Study: 100 ppm or 5 mg/kg/day; ICI Rat Study, < 500

ppm or \leq 25 mg/kg/day; the B-W Rat Study, 10 mg/kg/day. Based on the weight of evidence in all 3 rat studies, the non-oncogenic NOEL for rat is judged to be 5 mg/kg/day."

Overall Assessment of the Oncogenic Potential in Experimental Animals by EPA:

According to the International Agency for Research on Cancer (IARC), "the widely accepted meaning of the term 'chemical carcinogenesis' --- is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found". EPA considers this definition and the following 7 criteria to evaluate oncogenicity [by PT] in experimental animals when multiple oncogenic studies are available.

1. Oncogenicity in different (a) species, (b) strains, (c) sexes and (d) organs
2. Presence of rare neoplasms & numbers of different types of neoplasms in one or more species
3. Increased incidence of malignant neoplasms
4. Decrease in latency (time to tumor discovery)
5. Dose response relationship
6. Mutagenicity tests (See * below.)
7. Spontaneous tumor incidence in untreated animals

For discussion of all of the above, the reader is referred to the EPA report, pages 21-26.

* "A battery of mutagenicity tests has been performed on Permethrin to detect gene mutation, chromosomal aberrations and primary DNA damage. These tests included studies on S. typhimurium and E. coli (with & without activation), mouse lymphoma, dominant lethal, rat cytogenetics, mitotic recombination in yeast, DNA repair in E. coli and B. subtilis and unscheduled DNA synthesis in human fibroblasts. In none of these studies has Permethrin shown a mutagenic potential.

The mechanism of tumor induction by Permethrin apparently does not operate by biological mechanisms which directly involve the genetic integrity of the cell."

For the "Summary & Evaluation of Criteria Data" by EPA, please see copies of pages 27-31 of the EPA report, attached to this review (Appendix I).

Comments on Carcinogenic Studies:

The applicant submitted to FDA actual reports of only 2 carcinogenicity studies (B-W mouse & rat studies; see Pharm. Rev. of IND dated 3/31/83). However, they have submitted, in this NDA report, the review of EPA which encompasses the above-mentioned studies and in addition, 5 (3 mouse, 2 rat) other carcinogenicity studies. Based on the data submitted only to FDA, I had concluded that PT was not found to be tumorigenic in either species. Both EPA & I arrived at the same conclusion regarding the B-W rat study. However, EPA does not entirely share my conclusion about the mouse study, although the incidence of lung tumors in the high-dose females was within historical control range (see p. 17 of IND review). On page 26 of their review, EPA states the following: "Comparison of the observed lung tumor incidences in the three long-term mouse studies with the historical control incidences for either sex raises the possibility that these tumors may not be directly related to the ingestion of PT, but rather, may be simply an expression of the variability of the spontaneous and naturally occurring incidence of this lesion in mice. This is particularly true for males for which no tumor/dose relationships were found. Toxicology Branch recognizes some merit in this point of view. However, the definite lung tumor-dose relationship found for the females in the FMC-II Mouse Study and the lung tumor-dose related trend for the females in the B-W Mouse study cannot be ignored. Toxicology Branch considers the lung tumor incidences observed in females in these two studies to be supportive of one another." It is therefore apparent that EPA had more mouse data (than FDA) in arriving at the above conclusion, which deserves merit in my opinion.

It is my opinion that the EPA review/report is extremely thorough and comprehensive and I share the opinion of EPA reviewers concerning the oncogenic potential of PT, which states "that PT's potential for induction of oncogenicity in experimental animals is low and that the likelihood of oncogenic effects in humans is nonexistent or extremely low." Therefore, I see no reason for requesting submission of the data (5 additional carcinogenicity studies) not submitted to FDA, since I support the conclusions of EPA. Moreover, PT Creme Rinse 1% will most probably be used only once or twice in the lifetime of a human.

Evaluation/Overview

Clinical Use: Permethrin Creme Rinse 1% will be used as a pediculicide (single application, retreatment may be required for less than 1% of the patients). Permethrin, the active ingredient, is a synthetic pyrethroid.

Foreign Studies: The majority of the preclinical pharmacology/toxicology studies were performed abroad and are considered pivotal to a conclusion with regard to safety. These included various types of studies, e.g., acute toxicity, subchronic & chronic toxicity, reproduction, mutagenicity & carcinogenicity studies (see list on pages 3-5 of this review).

Overview (highlights) of Preclinical Toxicity Evaluation: In mice & rats treated IP with doses of permethrin (PT) up to 1000 mg/kg, the drug was relatively well-tolerated and the LD50 value in both species was greater

than 1000 mg/kg. In rats treated PO with 1% PT Creme Rinse, the LD₅₀ was greater than 5 g/kg. LD₅₀ values for mice & rats of PT formulated in different vehicles were:

<u>Species</u>	<u>Route</u>	<u>Formulation</u>	<u>LD₅₀ (mg/kg)</u>
Mice	PO		
	IV		
Rats	PO		
	Dermal		
	IV		

In rabbits, the LD₅₀ of 1% PT Creme Rinse applied dermally under occlusive dressing was greater than 2 g/kg. Rats exposed dermally for 24 hrs to a 40% w/v sol'n of PT in xylene showed no signs of toxicity clinically or at autopsy.

A study was carried out in rats dosed with PT (up to 15 days) at 6000 ppm of various cis-trans isomers (respectively, 25:75, 40:60 & 90:10%) to determine neurological effects. The severity of CNS symptoms (hyperexcitability, body tremors, flat-footed gait) appeared to be directly related to the cis isomer content. Both light & electronmicroscopy of the peripheral & CNS tissues were inconclusive in determining the etiology of the CNS disorders.

The sensitization potential of PT was assessed in dermally treated guinea pigs. PT was not a sensitizing agent in these test systems. Dermal irritation studies with PT in rabbits revealed that the test material was only mildly irritating. Applied to the rabbit's eye (0.1 ml of PT) was nonirritating, and an ocular hazard under normal conditions of use in humans was predicted to be highly unlikely.

PT w/w was formulated in several commercially available lotions (creme rinses) and these were applied once to dogs' hair at 50 g/dog. Samples of hair analyzed during 14 days of the study revealed that formulations containing PT left large conc'ns of PT on hair and that the addition of surfactants did not necessarily lead to a higher PT conc'n of the hair.

Absorption of topically applied ¹⁴C-permethrin (study performed by U.S. Armed Forces), as measured in excreta up to 7 or 14 days after application, was 30% in rabbits & 10% in dogs. Urinary excretion accounted for 75% of the radioactivity, usually within 24 hrs. Radiocarbon recovered in feces was always higher (2.5x) following cis PT application than for trans. It was estimated that absorption of PT in man should be less than 8% of the applied dose. The projected bioavailability to man from permethrin impregnated fabric (U.S. Army uniforms; 0.125 mg/cm²) would be less than 0.026 mg/kg/day.

Pharmacokinetic studies were carried out in rats dosed IV or dermally (several formulations) with PT. These studies revealed the following:

1. PT and/or its metabolites were extensively absorbed following dermal application.

2. Rat skin was an important site of PT metabolism and possibly conjugation, thereby limiting the systemic availability of the parent compound.
3. Metabolism of PT to the cis and trans DCVA's (trans or CIS - 3 (2,2 - dichlorovinyl)-2, 2-dimethylcyclopropane-carboxylic acid) was not dose-related, with higher doses favoring more DCVA formation.
4. Following application of 1% creme rinse, about 5% of the PT was absorbed into rat skin prior to washing at 10' after application.
5. After dosing with 5% dermal cream, the urinary excretion of the DCVA's tended to be fairly constant for several days and, therefore, the cream appeared to establish a "reservoir" for PT. However, washing 48 hrs after application removed most of the PT remaining in the skin.

In a number of mutagenicity test systems [S. typhimurium, E. coli, mouse lymphoma, dominant lethal, DNA repair in E. coli & B. subtilis, and unscheduled DNA synthesis in human fibroblasts] performed to detect gene mutations, chromosomal aberrations and primary DNA damage, PT was found to be nonmutagenic.

Teratology studies in mice, rats & rabbits at oral dosage levels up to 200 & 400 mg/kg/day of PT showed no potential for the drug to induce teratogenic effects. In a 3-generation reproduction study in rats with PT at dietary levels of up to 180 mg/kg/day, the drug produced no effect on growth, survival or reproductive ability, and there were no drug-related fetotoxic or teratogenic effects noted.

Oral toxicity studies in rats & dogs (3 & 6 months, respectively) revealed that doses up to 187 & 250 mg/kg/day were relatively well tolerated in both species. A higher dose in rats (357 mg/kg/day) caused hypersensitivity, decrease in body wt gain (M), increased liver wts & decreased thyroid wts.

Two carcinogenicity/toxicity studies in rats & mice were performed and submitted to FDA. Rats were dosed with PT at dietary levels of 0, 10, 50 & 250 mg/kg/day for 104 weeks. Drug-related effects of possible toxicological significance were: a higher mortality rate (HD, M); body tremors from week 90 on (HD gp); increases in liver wt (HD, M); dose-related increase in the incidence of periacinar hepatocytic hypertrophy (MD & HD gps) which was classified as work hypertrophy. Mice were dosed with PT at dietary levels of 0, 10, 50 & 250 mg/kg/day for 91 weeks. Drug-related effects of possible toxicological significance were increased kidney & liver wts in the HD group; however, there was no histological correlation. It was concluded that 10 & 60 mg/kg/day in the rat & mouse studies, respectively, were well tolerated.

There was no evidence of an oncogenic effect by PT in the rat study. In mice, there was a higher incidence of benign adenomas of the lung in the HD F compared to all F groups, including controls (statistically significant, $p < 0.01$, compared to control). However, most of the affected animals in all groups bore only a single adenoma and the mean size of tumors in the HD gp was similar to that in controls and other groups. In contrast, the incidence of

lung adenomas was higher in M controls than in the HD M. Also, the incidence of lung tumors in the F HD gp was within the historical control range and that of the F control gp was quite low compared to historical controls. Finally, in F there was no dose-related increase in incidence of malignant tumors or those bearing multiple lung tumors. In view of the aforementioned, it was concluded that this finding can be regarded as due to chance.

Permethrin and its metabolites have been approved by EPA as insecticide residues in or on certain raw agricultural commodities; see Appendix II (attached copy of Fed. Reg., Vol. 47, No. 195, Oct. 13, 1982). EPA evaluated 6 (3 mouse, 3 rat) long-term carcinogenicity studies; 2 of these were submitted to FDA and the EPA review/report on all 6 was also incorporated in this NDA and reviewed.

Based on evaluation of all available studies and numerous consultations/peer reviews, the following was concluded by EPA:

1. A low oncogenic potential was demonstrated in mice. Treated F had a higher tumor incidence than controls in terms of lung adenomas (250, 375, 750 mpk/day), adenocarcinomas (750 mpk/day) and hepatomas (375, 750 mpk/day).
2. There was no evidence of oncogenic potential in rats.
3. The likelihood of oncogenicity in humans is slight.

Recommendations: The following labeling changes are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Statement should be revised to read as follows:

Pregnancy: In the statement proposed by the applicant, insert in the first sentence after "and rabbits", in parentheses, the following:
 "(200-400 mg/kg/day, orally)."

cc: Orig. NDA
 HFN-815
 HFN-340
 HFN-815/GCDebbas/smc/8/5/85
 R/d init.by:JMDavitt
 Appendices (2) attached.
 0036p

HFN-815/MO
 CSO

Gamil Debbas

Gamil C. Debbas, Ph.D.

N19435

-2

NDA 19-435



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-435

MAR 31 1985

George M. Lyon, Jr., M.D.
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Dear Dr. Lyon:

Reference is made to your New Drug Application dated February 28, 1985, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nix (permethrin) Creme Rinse, 1%.

Reference is also made to your additional communications dated May 28, 1985, July 1 and 11, 1985, August 14, 1985, September 20, 1985, and March 26, 1986.

We have completed our review of this application including the submitted draft labeling and the application is approved. However, prior to marketing, the following changes must be made in the labeling:

1. The first sentence of the CLINICAL PHARMACOLOGY section should read as follows:

Permethrin is a synthetic pyrethroid, active against lice, ticks, mites, and fleas.

2. The second sentence of the second paragraph in the CLINICAL PHARMACOLOGY section should be revised as follows:

Although the amount of permethrin absorbed after a single application of the 1% Creme Rinse has not been determined precisely, preliminary data suggest it is less than 2% of the amount applied.

3. Because residual drug on hair was measured only up to ten days in the single application study, the last sentence of the second paragraph in the CLINICAL PHARMACOLOGY section should read as follows:

Residual persistence of Nix is detectable on the hair for at least 10 days following a single application.

4. The word "excellent" should be deleted from the first sentence of the "Pediculicidal/Ovicidal Activities" subsection of the CLINICAL PHARMACOLOGY section. In addition, the second sentence of this subsection should be revised to include the words "demonstrated at 14 days" after "head lice."

5. A third sentence should be added to the INDICATIONS section as follows:

If live lice are observed after at least seven days following the initial application, a second application can be given.

6. The Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section should read as follows:

Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of in vitro and in vivo genetic toxicity studies.

Permethrin did not have any adverse effect on reproductive function at a dose of 100 mg/kg/day orally in a three-generation rat study.

7. In the Pregnancy subsection of the PRECAUTIONS section, the first sentence should read as follows:

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin.

8. The second sentence of the Nursing Mothers subsection of the PRECAUTIONS section should read as follows:

Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

9. The HOW SUPPLIED section should state:

Nix (permethrin) 1% (wt./wt.) is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g.

10. The trade name Nix should be inserted where (Trade Name) was used in the draft labeling.

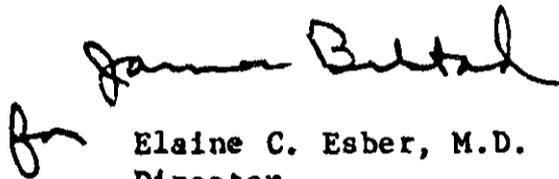
The labeling should be revised exactly as we have requested and twelve copies of the final printed version of the revised labeling must be submitted to FDA.

Because the data submitted do not allow a precise determination to be made of the amount of permethrin absorbed after a single application of the 1% Creme Rinse, we request that you conduct a post-marketing study to provide that information.

In addition, please submit in duplicate all advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products and a second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Also, when a market package is available, please send one to the Division of Anti-Infective Drug Products.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,



Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

FPL

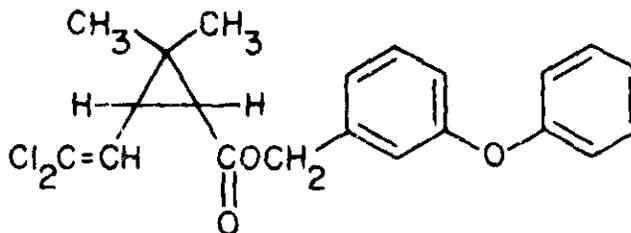
585030

NIX™
(PERMETHRIN) 1%
Creme Rinse



DESCRIPTION: Nix™ (Permethrin) 1% Creme Rinse is a topical pediculicide and ovicide for the treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). The product is a creme rinse, each gram containing Permethrin 10 mg (1%). Inactive ingredients are: stearylalkonium chloride, hydrolyzed animal protein, cetyl alcohol, polyoxyethylene 10 cetyl ether, hydroxyethylcellulose, balsam Canada, fragrance, citric acid, propylene glycol and FD&C Yellow No. 6. Also contains isopropyl alcohol 200 mg (20%) and added as preservatives, methylparaben 2 mg (0.2%), propylparaben 0.8 mg (0.08%) and imidazolidinyl urea 2 mg (0.2%).

Permethrin is a mixture of the *cis* and *trans* isomers of the synthetic pyrethroid (+-)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (*cis/trans*/25:75). It is a yellow to light orange-brown low melting solid or viscous liquid. The molecular weight is 391.29 and the structural formula is:



CLINICAL PHARMACOLOGY: Permethrin is a synthetic pyrethroid, active against lice, ticks, mites, and fleas. It acts on the nerve cell membrane to disrupt the sodium channel current by which the polarization of the membrane is regulated. Delayed repolarization and paralysis of the pests are the consequences of this disturbance.

Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine. Although the amount of permethrin absorbed after a single application of the 1% Creme Rinse has not been determined precisely, preliminary data suggest it is less than 2% of the amount applied. Residual persistence of Nix is detectable on the hair for at least 10 days following a single application.

PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovicidal activity against *Pediculus humanus var. capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovicidal activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative

NIX™ (PERMETHRIN) 1% CREME RINSE

data for interpreting results from carcinogenicity bioassays in rodents were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies.

Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

OVERDOSAGE: No instance of accidental ingestion of Nix has been reported. If ingested, gastric lavage and general supportive measures should be employed.

DOSE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)

Store at 15°-25°C (59°-77°F).

NIX™ (PERMETHRIN) 1% CREME RINSE

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Medical Review

MEDICAL OFFICER'S REVIEW OF NDA 19-435
ORIGINAL SUBMISSION

Date: October 2, 1985

SPONSOR: Burroughs Wellcome Co.
Research Triangle Park, NC

DRUG: Permethrin creme rinse 1%

CLINICAL INDICATION: Pediculosis capitis (head lice)

FORMULATION:

DATE OF SUBMISSION: February 28, 1985,

CONTROLS REVIEW:

PHARMACOLOGY REVIEW: Dr. Gamil Debbas has recommended revision of the pharmacology section of the labeling, but did not have objections to approval of the NDA.

HISTORY AND RATIONALE FOR USE: Permethrin is chemically and pharmacologically related to the naturally occurring pyrethrins, insecticides which are derived from the chrysanthemum. It is one of a large number of synthetic analogs of pyrethrin known as pyrethroids, which have been developed to increase the insecticidal potency and overcome the photochemical instability of pyrethrin. Introduced in 1973, permethrin is stated to be the first relatively stable pyrethroid with an insecticidal potency 50 to 100 times greater than the pyrethrins.

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The insecticidal mechanism of the pyrethrins and the pyrethroids appear to be the same. They are neurotoxins which act primarily on physicochemical processes rather than on biochemical ones. It has been demonstrated in both vertebrate and invertebrate systems that the intact molecule is required for neurotoxic activity. The very low mammalian toxicity of the pyrethrins, especially as compared with other classes of insecticides, is partly attributed to rapid esterase hydrolysis of the molecule by the ubiquitous plasma and tissue esterase activity in mammals, including man. The natural pyrethrins also rapidly undergo photodecomposition to inactive products in the presence of oxygen and ultraviolet light.

The sponsor feels that permethrin creme rinse has significant advantages over the other formulations used for the treatment of head lice in the US, which contain either lindane (gamma-benzene hexachloride), malathion, or natural pyrethrins, because of the relative safety, greater effectiveness, and the convenience of a single application.

In vitro studies

Preliminary studies on solutions of 0.01-1.0% permethrin showed effective pediculicidal and ovicidal activity of the 0.5% and 1.0% concentrations against *Pediculus humanus var. capitis*. The effect of various organic solvents was studied, and it was found that permethrin in isopropanol had potent ovicidal activity.

Professor David Taplin of the University of Miami performed studies on a number of formulations containing 1% or 5% permethrin and varying amounts of organic solvents in conventional shampoo and hair conditioner (creme rinse) formulae. A vehicle control for each formulation was included, as were a water control, a dry control, and Kwell shampoo. The shampoo formulations were found to be unsuitable, as they were unstable with the organic solvents, and without the solvents the permethrin did not dissolve.

The methodology for Prof. Taplin's study was adapted from the 1975 World Health Organization document entitled "Instructions for Determining the Susceptibility or Resistance of Body Lice and Head Lice to Insecticides". For the determination of adult pediculicidal activity, at least ten adult lice from infested subjects were exposed to cloth impregnated with the test formulations. The lice were observed for activity at 10, 30, 60, and 120 minutes, and at 4 and 24 hours. To determine ovicidal activity, a minimum of 20 hairs with attached viable nits were dipped for five minutes in each test formulation. They were then rinsed with clear water, dried, and incubated for 14 days.

Pertinent results were as follows. Pediculicidal activity is expressed as the percent of adult lice killed at each observation time. Ovicidal activity is expressed as the percent of unhatched nits observed at 14 days.

Clinical safety studies

The clinical safety studies on the 1% Permethrin creme rinse consisted of a sensitization study and topical and systemic tolerance and absorption studies after a single application and after multiple applications. Phototoxicity and photosensitization studies were done on a 5% permethrin cream. The studies were conducted by James Leyden, M.D., and Kays Kaidbey, M.D., of the Department of Dermatology, University of Pennsylvania. Additional information on safety includes adverse reactions which occurred in the clinical effectiveness studies, studies performed in England on other permethrin formulations, and a literature review of clinical trials of permethrin.

1) Sensitization: A maximization test was performed on 37 subjects. After pre-treatment of a skin site with 2% sodium lauryl sulfate, application of the 1% Permethrin creme rinse was made under an occlusive patch for 48 hours. This procedure was repeated for a total of five applications to the same skin site over a period of 10 days. After pre-treatment of a new skin site with 10% sodium lauryl sulfate for one hour, the test product was applied under occlusion for 48 hours. The site was then similarly treated for an additional 24 hours. Twelve of the subjects were also simultaneously treated with Kwell Lotion and RID.

Results were that no reactions occurred with any of the test products.

2) Phototoxicity and photosensitization: In the phototoxicity study, applications of 5 ul/cm² of a 5% permethrin cream were made to delineated skin sites of 10 subjects, followed by occlusion for 6 hours. The sites were then exposed to long wave ultraviolet and visible light at a dose of 20-25 joules/cm². One control site was similarly treated but not irradiated, and a second control site was treated with the cream vehicle and irradiated. No reactions were found.

The photosensitization study was performed on 25 subjects. In the induction phase, 10 ul/cm² of a 5% permethrin cream was applied with occlusion for 24 hours. After removal of the patch, the site was immediately exposed to 3 MED of ultraviolet light. This procedure was repeated to the same skin site for a total of six exposures over a period of three weeks. The challenge was conducted ten days after the last exposure. Application of 5 ul/cm² of the test material was made to a new skin site, followed by occlusion for 24 hours. The site was then exposed to 4 joules/cm² of long wave ultraviolet. A similarly treated but unirradiated site served as a control. The sites were examined 72 hours later for erythema and edema. Results were that there were no reactions during either the induction or challenge phase.

The sponsor states that although these studies were performed with a formulation which differed from that of the Permethrin creme rinse, it is felt that these results are directly applicable to the Permethrin creme rinse, since the ingredients in the rinse other than the permethrin are known to be free of phototoxic or photoallergenic potential.

3) Topical and systemic tolerance and absorption after a single application:
This study was performed on 10 subjects. Following a shampoo with Prell and a clear water rinse, the hair was dried, and Permethrin creme rinse 1% was applied in a sufficient amount to saturate the hair and scalp (25-50 cc). The rinse was left on the hair for 10 minutes and then rinsed out with clear water. The subjects did not shampoo for 24 hours after application of the creme rinse, but resumed their normal hair grooming practices thereafter.

The subjects were evaluated at 24 hours and at 7 days after application for subjective complaints and objective abnormalities of the scalp and adjacent skin. The following clinical laboratory tests were done prior to application, and at 24 hours and 7-10 days after application: CBC with differential, Hgb, SGOT, SGPT, LDH, AP, bilirubin, total protein, albumin, BUN, creatinine, uric acid, glucose, cholesterol, triglycerides, electrolytes, and urinalysis. Hair samples for measurement of permethrin levels were obtained at 24 hours and at 7-10 days after application. Urine and plasma were examined for permethrin and/or metabolites for 7-10 days after treatment.

Results were that there were no abnormalities of the scalp or skin, and no subjective complaints were reported. There were no consistent laboratory abnormalities found, and none were considered to be drug-related.

The detection limit for drug in the plasma was 5 ng/ml. Of 70 plasma specimens assayed for drug, only one had detectable levels of permethrin. The concentrations were 20.5 and 6.3 ng/ml of cis- and trans-permethrin, respectively. This was a 2 hour post-treatment specimen, the subject did not subsequently show detectable plasma levels or metabolites in the urine, and it was thought that inadvertent contamination might have occurred. In the urine assay the detection limit for metabolites was 2.5 ng/ml. Measurable levels of metabolite, in a range of 22.4 - 47.2 ng/ml, were found in 9 of 59 urine samples, with no detectable levels in the 7-10 day samples. All of the subjects had measurable levels in the hair throughout the 10 day period, with the levels at 7-10 days approximately 10-50% of those at the 24 hour period.

4) Topical and systemic tolerance and absorption after multiple applications:
This study was performed on 10 subjects, using the same procedure as in the single application study. Following a shampoo with Prell and a clear water rinse, the hair was dried, and Permethrin creme rinse 1% was applied in a sufficient amount to saturate the hair and the scalp (25-50cc). The rinse was left on the hair for 10 minutes and then rinsed out with clear water. This was repeated weekly for 8 weeks. The subjects were not permitted to shampoo for 24 hours after each application, but were otherwise permitted to continue their usual hair grooming practices. The subjects were evaluated at one and two weeks after the last application.

Prior to each application and at the followup visits the subjects were evaluated for subjective complaints and objective abnormalities of the scalp and adjacent skin. Hemograms and clinical chemistries as in the single

application study were done prior to the first, fourth and eighth applications. Hair samples for permethrin levels, and urine and plasma for permethrin and/or metabolites were obtained during the course of the study and in the followup period.

There were no abnormalities of the scalp or skin, no subjective complaints, and no significant laboratory abnormalities. Detectable plasma levels of permethrin, in a range of 5 - 20 ng/ml, were found in two samples from week 6 and three samples from week 8. Detectable urine levels of 2.5-25 ng/ml of metabolites were found in one sample at week 8. Results of the hair sample assays were similar to those in the single application study, with no accumulation of drug found, and a decrease in levels of approximately one-third at two weeks after the last application.

The sponsor was asked by this reviewer to estimate the percentage of applied drug that was absorbed in these studies, and the sponsor has provided this information in the submission of 9/26/85. Because there was only one plasma sample with quantifiable levels of permethrin, and urine samples had levels of metabolites mostly below quantifiable levels, the sponsor based the estimation upon assumptions and extrapolations from studies on other topical permethrin formulations and oral permethrin. Their estimation for the amount of permethrin absorbed when 50cc of the 1% permethrin rinse is applied to the scalp is 1.6% of the applied dose, or 7.8 mg permethrin.

5) Adverse reactions in clinical effectiveness studies: The clinical effectiveness studies consisted of a single investigator study in which 29 patients were treated with Permethrin creme rinse, and a multicenter study in which 260 patients were treated with the rinse. There were no adverse reactions reported in the first study. In the second study the nature and frequency of adverse reactions with permethrin were comparable to that in the control group treated with Kwell, and consisted of symptoms such as burning/stinging, tingling, numbness, or scalp pain in 3%, mild scalp irritation in a few patients, and a transient rash in one patient. These are described further under the review of the clinical effectiveness studies.

6) Studies on other permethrin formulations: Clinical tolerance and absorption studies were performed on two other formulations of permethrin, a lotion and an aerosol, by the Wellcome Foundation Ltd. in England. The lotion contained 1% permethrin in 89% isopropanol and the aerosol contained 0.67% permethrin in odorless paraffin. The permethrin was present as 25% cis and 75% trans forms, as in the creme rinse formulation.

An absorption study on the lotion was performed on 10 subjects. Application was made in a sufficient volume to wet the hair, which then dried naturally. The hair was washed 24 hours later. Urine and hair assays for permethrin and/or metabolites were performed for 14 days after application. Three subjects developed a mild, patchy erythema which faded in a few days. Based on the urine assays, it was estimated that from 0.6 - 2.5% of the applied dose was absorbed and excreted. The concentration of permethrin remaining on the hair 14 days after application ranged from 2% to 23% of the amount measured immediately after application.

An absorption study on the aerosol was performed on 10 subjects, using a procedure similar to that in the lotion study. One subject developed a mild patchy erythema which was still present at day 7, and one developed a mild transient seborrheic dermatitis. Based on the urine assays, it was estimated that 0.9% of the applied dose was absorbed and excreted.

A preliminary study on the local tolerance and effectiveness of the lotion and aerosol was performed by Professor David Taplin in Panama on 60 patients with head lice. The patients were treated with either the active lotion or placebo lotion for 30 minutes or two hours, or with the active or placebo aerosol for two hours or four hours. Only 1 of 20 patients treated with the active lotion, and 1 of 20 treated with the active aerosol had live lice present at 14 days after application, as compared with 17 of 20 placebo treated patients. No adverse reactions were reported.

A multicenter comparative clinical trial was performed in England on 385 children with head lice. Of these, 195 were treated with 1% permethrin lotion, 144 with Prioderm (0.5% malathion), and 46 with Derbac (0.5% malathion). The permethrin lotion was applied for two hours and the malathion products for twelve hours. The scalps were examined for irritation and live lice at 24 hours, 7 days, and 6 weeks after treatment. Infestation after treatment was found in 3 patients (1.5%) treated with permethrin, in 5 patients (3.5%) on Prioderm, and in 1 Patient (2.2%) on Derbac. Adverse reactions were reported in about 7% of each treatment group, these were similar in each group and consisted of eye or scalp burning or stinging, and 1 - 2 cases each of hair loss, headache, nausea, and GI upset.

An additional multicenter clinical trial was performed in England on 568 children with head lice. Of these, 298 were treated with the permethrin 0.67% aerosol, 176 with Prioderm, 67 with Derbac, and 27 with Carylderm (0.5% carbaryl). The permethrin aerosol was applied for two hours and the other products for twelve hours. The scalps were examined for irritation and live lice at 24 hours, 7 days, and 6 weeks after treatment. Infestation after treatment was found in 12 patients (4%) on permethrin, 4 (2.3%) on Prioderm, 2 (3%) on Derbac, and in 4 (14.8%) on Carylderm. Similar adverse reactions were reported in 9% on permethrin, 6% on Prioderm, and in 44% on Carylderm, these consisted of eye or scalp burning or stinging, red sore patches on the scalp or neck, and one case each of headache, faintness, facial erythema, and epistaxis.

7) Literature review: There are no published studies on the use of permethrin for the treatment of head lice; however, it has been used for body lice and scabies, and as a protective by clothing impregnation or spray.

One report was on the use of 1% permethrin talc (25:75 cis:trans) to treat body lice infestations in 300 inhabitants of an Egyptian village. The powder was blown through the sleeves and collar and around the neckband of each patient's clothing, in an amount of 30-50 gm/person. The patients were examined at intervals for one month. The infestation rate prior to treatment was greater than 60%. On day 8 after treatment the infestation rate was 2%, as compared to an infestation rate of 68% in a control population. No adverse reactions were reported.

A further study in three similarly infested Egyptian villages compared treatment with 50 gm of either 2.5 gm/kg or 5 gm/kg permethrin powders to untreated controls. Administration was in the same manner as in the previous study. The patients were examined at 2 weeks and three months after treatment. At two weeks 99% and 100% of the patients were free of lice in the groups treated with the 2.5 gm/kg and 5 gm/kg powders, respectively, while the untreated group remained the same. No adverse reactions were reported.

A comparative trial of permethrin and lindane was performed in patients with scabies in Rhodesia. Administration was a single whole body application of 2% lindane in liquid paraffin to 134 patients and 1% permethrin in liquid paraffin to 95 patients. Followup examination at 2-3 weeks on 32 patients treated with lindane and 38 treated with permethrin showed a cure rate of about 60% in both groups. No adverse reactions were reported.

Studies have been performed by the U.S. Army and the U. S. Department of Agriculture on the use of permethrin-impregnated clothing (0.125 mg/cm^2) as a protectant against chigger mites, for which effectiveness was reported with no adverse reactions. There have also been several other reports of the effectiveness of permethrin impregnated clothing and aerosol sprays against various arthropods; no adverse reactions were reported in these studies.

Effectiveness studies

The clinical studies consisted of a single center study performed in Panama and a multicenter domestic study.

Study I. This study was performed by the following co-investigators:

Professor David Taplin
Department of Dermatology
University of Miami School of Medicine
Miami, FL

Pedro Castillero, M.D.
Ministry of Health
Panama City, Panama

The conduct of the study was as follows.

- 1) Study design: This was a double blind parallel group comparison of 1% Permethrin creme rinse with placebo (the vehicle) in patients infested with *Pediculus humanus var. capitis*, with random assignment of patients to the two treatment groups. A third concomitant but non-blinded arm of the study was a group treated with Kwell shampoo (1% lindane).
- 2) Patient selection: The patients were primarily children of an indigenous Indian population, in whom the diagnosis was established by the identification of live adult lice or nymphs. The presence of nits only was not acceptable.
- 3) Patient exclusions: Patients were excluded if they had used any other pediculicide within one week prior to the study, or if they were taking any anti-infective medication.
- 4) Treatment regimen: After a shampoo with Prell, the creme rinse formulations were applied in sufficient quantity, from 10 to 50 cc, to saturate the hair and scalp, and remained for 10 minutes on the scalp before being rinsed out with clear water. The Kwell shampoo was applied to dry hair for 4 minutes, then lathered and rinsed out. Nits were not combed out of the hair after treatment. The patients did not shampoo their hair for 24 hours after treatment, and did not use any other hair grooming aid, medicated shampoo, or pediculicide during the course of the study.
- 5) Effectiveness parameters: The patients were observed for the presence or absence of live adult lice or nymphs at 1, 2, 4, 6, and 24 hours, and 7 and 14 days after treatment. Ten hairs with apparently viable nits were also taken for incubation immediately after treatment.
- 6) Tolerance evaluation: At each followup visit, an assessment of the presence or absence of the following symptoms and signs was made: pruritus, burning/stinging, pain, numbness, tingling, edema, erythema, or rash.

Results were as follows.

- 1) Demographic characteristics: Ninety-three patients were enrolled in the study, of which 29 were treated with 1% Permethrin creme rinse, 34 were treated with placebo, and 30 were treated with Kwell. It is stated that there were no differences between treatment groups in regard to age, sex, and hair characteristics such as texture, length, and curliness. Almost all patients were considered to have heavy louse infestations prior to treatment, defined as the presence of more than five adult lice or nymphs.

2) Pediculicidal and ovicidal effect: The number and percentage of patients that were free of adult lice or nymphs at the 7 and 14 day evaluations were as follows.

	<u>Pediculicidal rates</u>		
	<u>7 days</u>	<u>14 days</u>	<u># pts</u>
Permethrin	29 (100%)	28 (97%)	29
Placebo	3 (9%)	2 (6%)	34
Kwell	20 (67%)	13 (43%)	30

It was felt that the frequency of Kwell treatment failures was higher than would be expected in the U.S., probably due to a high frequency of resistance to organochlorides among insects in general in Central America.

The viable nits obtained prior to treatment showed a hatch rate of over 90% in all three groups. The mean percentages of nits obtained immediately after treatment that subsequently hatched on incubation were as follows:

<u>Mean hatch rates</u>	
Permethrin	30%
Placebo	86%
Kwell	55%

The differences between groups in pediculicidal and ovicidal activity was stated to be highly statistically significant.

In only three of the 29 patients treated with permethrin did none of the post-treatment nits hatch on incubation. It was therefore concluded that the clinical effectiveness at 14 days was due to the residual permethrin on the hair shaft, and that the residual pediculicidal activity may be more important than the ovicidal activity.

3) Tolerance: No subjective complaints or objective adverse effects were reported.

Study II. This study was performed by the following investigators.

Joan DiNapoli, R.N., Ph.D.
Consultation and Research, Inc.
Durham, NC

Joseph Orthoefer, DVM, MPH
Winnebago Department of Public Health
Rockford, IL

Lawrence Parish, M.D.
Paddington Testing Co., Inc.
Philadelphia, PA

Doris Wagner, R.N., M.S.
Marion County Health Department
Indianapolis, IN

Steven Englander, M.D., MPH
Department of Health Sciences
Phoenix, AZ

Kathie Brandenburg, R.N., MS
City of Nashua Community Health Department
Nashua, NH

Amos Deinard, M.D.
University of Minnesota Hospitals
Minneapolis, MN

The conduct of the study was as follows.

1) Study design: This was a single blind (investigator blind) parallel group comparison of 1% Permethrin creme rinse and Kwell shampoo in the treatment of head louse infestations. Persons who were the initial patient in a family were designated 'index cases', and were randomly assigned to one of the treatment groups. Whenever possible, other family members were evaluated, and if afflicted, were treated with the same medication as the index case.

2) Patient selection: The patients were primarily children, in whom the diagnosis was established by the identification of live adult lice or nymphs. The presence of nits only was not acceptable.

3) Patient exclusions: Patients were excluded if they had any other abnormal scalp or hair condition, or if any other pediculicide had been used within one week of the the study.

4) Treatment regimen: After a shampoo with Prell, a sufficient quantity of Permethrin rinse (25-50 cc) was applied to saturate the hair and scalp, and remained for 10 minutes before being rinsed out with clear water. In the alternate group Kwell shampoo was applied to the dry hair in sufficient quantity to saturate the hair (25-50 cc), remained for 4 minutes, and was then lathered and rinsed out; this was in accord with the manufacturer's directions. Nits were not combed from the hair after treatment. The patients did not shampoo their hair for 24 hours after treatment, and did not use any other hair grooming aid, medicated shampoo, or pediculicide during the study.

5) Effectiveness parameters: Followup evaluations were done by a staff member other than the one who had administered treatment at 24 hours, 7 days (range 5-10 days), and 14 days (range 12-16 days). Each patient was examined for five minutes for the presence or absence of live adult lice or nymphs, apparently with an illuminated macromagnification technique.

6) Tolerance evaluation: At 30-60 minutes after treatment and at each subsequent return visit an assessment for the following symptoms and signs was made: rash, erythema, edema, pruritus, burning/stinging, numbness, tingling, or scalp discomfort.

In evaluating the results, the sponsor found that the patients were not properly randomized in one study, that of Dr. Orthoefer, and that the blind may have been broken when the medication was distributed, in an effort to treat all the children at a particular school with Permethrin. For this reason the sponsor analysed the results with and without the Orthoefer study.

Because of the high rates of effectiveness shown with Permethrin in the pooled results, this reviewer did not feel that there was a need for review of the individual studies. The results were as follows.

Pooled results

1) Demographic characteristics: A total of 577 patients were enrolled in the study, of which 331 were index cases, i.e., randomly assigned to treatment. Of these, 512 patients, including 292 index cases, were fully evaluable for effectiveness at 14 days.

The demographic characteristics were as follows.

	<u>Permethrin</u>	<u>Kwell</u>
<u>No. of pts</u>	290	273
<u>Age</u>		
1-5	49 (17%)	53 (20%)
6-10	156 (54%)	136 (50%)
11-15	39 (13%)	38 (14%)
16-20	2 (1%)	6 (2%)
> 20	43 (15%)	39 (14%)

	<u>Permethrin</u>	<u>Kwell</u>
<u>Sex</u>		
Female	175 (60%)	178 (65%)
Male	115 (40%)	95 (35%)
<u>Race</u>		
White	256 (88%)	229 (84%)
Black	0 (0%)	4 (1%)
Hispanic	16 (6%)	18 (6%)
Other	18 (5%)	22 (10%)
<u>Hair texture</u>		
Fine	82 (28%)	70 (26%)
Average	179 (62%)	176 (64%)
Coarse	29 (10%)	27 (10%)
<u>Hair curliness</u>		
Straight	228 (79%)	226 (83%)
Curly	61 (21%)	45 (16%)
Kinked	1 (0%)	2 (1%)

The baseline infestation rates were as follows.

	<u>Baseline infestation</u>		
	<u>1-5 lice</u>	<u>> 5 lice</u>	<u># pts</u>
<u>All patients</u>			
Permethrin	216 (83%)	44 (17%)	260
Kwell	195 (77%)	57 (23%)	252
<u>Index cases</u>			
Permethrin	122 (82%)	27 (18%)	149
Kwell	104 (73%)	39 (27%)	143

(The above table is from the statistical report, and is at variance with the summary report; the latter appears to be in error.)

It was found that 13 patients inadvertently had been treated twice, and one had been treated three times, for reinfestations. Only the first entry of these patients was included in the analysis of results. (Nine of the 13 were originally treated with Kwell and four with Permethrin, all had been free of lice at the 14 day evaluation). The sponsor was asked by this reviewer to provide

a further explanation of the dropouts than was given in the original submission, and this information has been provided in the submission of 9/26/85. The summation of reasons for exclusion from the efficacy analyses, for both index cases and for all patients, is as follows.

	<u>Index pts</u>	<u>All pts</u>
No. patients entered	331	
No. patients excluded		577
Second entry	9	13
Third entry	1	1
Protocol violations	4	7
Dropouts, reasons unrelated	7	11
Dropouts, reasons unknown	18	33
Total pts excluded	39	65

Of the 33 dropouts for unknown reasons, 13 (8 index) were in the Kwell group, and 20 (10 index) were in the Permethrin group.

The number of evaluable patients per investigator was as follows.

	<u># pts</u>
DiNapoli	156
Orthoefer	94
Parish	4
Wagner	97
Englander	82
Brandenburg	24
Deinard	55

Investigator DiNapoli conducted studies at three centers, so that nine separate centers were involved in the study.

2) Pediculicidal effect: The number and percentage of patients that were free of live adult lice and nymphs at the day 7 and 14 evaluations were as follows.

	<u>Pediculicidal rates</u>	
	<u>Kwell</u>	<u>Permethrin</u>
<u>All patients</u>		
Day 7	228/248 (92%)	259/260 (99%)
Day 14	215/252 (85%)	257/260 (99%)
<u>Index cases</u>		
Day 7	133/143 (93%)	148/149 (99%)
Day 14	121/143 (85%)	148/149 (99%)

The most meaningful comparison was felt to be that of the results at 14 days with the index cases; statistical analysis showed Permethrin to be significantly superior to Kwell in this parameter ($p < 0.001$).

Results at the individual centers for the index cases were as follows. At two of the centers all patients were cured, and at all seven of the other centers the proportion cured was greater in the Permethrin group. The differences were statistically significant in two of the centers ($p < 0.005$).

Of the 13 patients treated for reinfestations, 11 were treated with Permethrin and 2 with Kwell, one treatment failure occurred in a Permethrin patient who had previously been successfully treated with Kwell.

Tabulation of the data with omission of the Orthoefer study, which had not been properly randomized and blinded, was as follows.

	<u>Pediculicidal rates</u>	
	<u>Kwell</u>	<u>Permethrin</u>
<u>All patients</u>		
Day 7	199/217 (92%)	193/194 (99%)
Day 14	188/222 (85%)	193/196 (98%)
<u>Index cases</u>		
Day 7	105/113 (93%)	106/107 (99%)
Day 14	95/114 (83%)	108/109 (99%)

Statistical analysis of the results for the index cases at 14 days showed Permethrin to be significantly superior to Kwell ($p < 0.001$).

3) Adverse reactions: All 577 patients entered into the study had at least one evaluation following treatment, and thus all provided information on safety. The occurrence of the symptoms and signs which were assessed at each visit was divided into three categories, as follows.

a) Pruritus alone which appeared or was aggravated after treatment was regarded as primarily disease-related. This was reported in 17 (6%) of the Permethrin group and in 13 (5%) of the Kwell group.

b) Symptoms other than or in addition to pruritus (burning/stinging, tingling, numbness, or scalp pain) which appeared or were aggravated after treatment were regarded as possibly drug-related; these were reported in 10 (3%) of the Permethrin group and in 10 (4%) of the Kwell group.

c) Objective signs (erythema, edema, rash) which appeared or were aggravated after treatment were regarded as probably drug-related; these were reported in 6 (2%) of the Permethrin group and in 8 (3%) of the Kwell group.

Nearly all of the above adverse experiences were mild and transient. One case of burning/stinging with Permethrin and one rash with Kwell were reported as moderate in severity, and one case of tingling with Kwell was reported as severe. The six category c adverse reactions in the Permethrin group were as follows: a mild papular rash in 1 patient which had resolved by 7 days, mild scalp redness in 3 patients, and mild redness and edema in 2 patients. The eight category c reactions in the Kwell group were as follows: mild erythema in 4, mild rash in 3, and a moderate rash in 1 patient.

Adverse experiences apart from the protocol assessments which were possibly related to treatment were reported in three of the Permethrin group and in two of the Kwell group. These were transient headache in 1, and scabs of the scalp presumed due to excoriation in 2 of the Permethrin group, and a rash and an open lesion of the scalp in 1 patient and hives in another patient in the Kwell group.

The incidence of reported adverse reactions varied considerably among the different centers. In three of the seven centers no adverse reactions were reported. The largest number, 31 reactions, and proportion, 29% of the treated group, were reported by the center at Indianapolis. The incidence of reactions in the remaining centers varied between these numbers.

In a separate ongoing study on prophylaxis, one patient developed a severe rash of the neck and shoulders after application of the Permethrin rinse vehicle, and later had a more severe reaction when the patient subsequently used the Prell shampoo that she had obtained in the study. The sponsor feels that patients should be advised to use a shampoo product with which they are familiar in conjunction with the use of Permethrin rinse.

Labeling review: The product is for prescription use. The trade name has not yet been determined. The directions for use are for a single application of an amount sufficient to saturate the hair and scalp, to remain for 10 minutes before being rinsed with water.

The package insert is felt to be satisfactory.

Summary and evaluation

It is felt that the product is safe and effective for the proposed clinical use.

Safety: The clinical safety studies consisted of a sensitization study and topical and systemic tolerance and absorption studies after single and multiple applications. No sensitization was found. In the systemic absorption studies, no adverse cutaneous reactions or laboratory abnormalities were found after single application or after eight weekly applications to groups of 10 subjects each, with applications made according to the proposed clinical use. It was estimated that about 1.6% of the applied dose of permethrin was absorbed.

In the clinical effectiveness studies, done on about 600 patients, the nature and frequency of adverse reactions with Permethrin were comparable to those in the control group treated with Kwell.

Effectiveness: The effectiveness studies consisted of a double blind comparison with the vehicle in a single center study, and a single blind (investigator blind) comparison with Kwell in a multicenter study.

The first study was conducted on 63 patients. The parameters for effectiveness were observation for adult lice or nymphs for 14 days after treatment, and the incubation of ova taken immediately after treatment to determine viability. Permethrin was significantly superior to the vehicle in both pediculicidal and ovicidal rates. The pediculicidal rate was very high, 97% at 14 days, but the ovicidal rate, 70% of the sampled nits, was less satisfactory. (A third arm of this study was a non-blinded comparison with Kwell; although results with Permethrin were much superior to those with Kwell, these were not considered to be valid because of a probable resistance to Kwell in this Central American country).

The second study was performed by seven investigators on 512 evaluable patients at nine centers. This included 292 'index cases'; an index case was the initial patient in a family, who was randomized to one of the treatment groups. The remaining patients were other afflicted family members who were treated with the same medication as the index case. The parameter for effectiveness was observation for adult lice or nymphs at 7 and 14 days after treatment; the ovicidal effect was not determined.

In the pooled results, the pediculicidal rate at 14 days with Permethrin rinse was very high, 99%, and was significantly superior to that with Kwell. The effectiveness was apparent at each of the nine centers; all patients were cured in two centers, and the cure rate was greater in the Permethrin group at each of the other seven centers, with results at two centers showing a statistically significant difference.

The incubation period for head lice ova is generally considered to be 6 to 8 days. To confirm this, we consulted Prof. David Taplin of the University of Miami, a recognized authority, who stated that all ova would have hatched during the 14 day period.

The results of the two studies indicate that Permethrin rinse has a greater pediculicidal than ovicidal effect, which is to be expected, as ova are more difficult to treat. In addition to a direct ovicidal effect, the effectiveness on ova is apparently due to residual amounts of the drug in the scalp which are cidal to emerging nymphs. Previous clinical studies confirmed that detectable amounts of drug remained on the hair for ten days after application.

Recommendations: It is recommended that the application be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA

HFN-815

HFN-815/DCBostwick

HFN-815/PHuene

4491b

ET 11/19/85
HFN-340
C.C.E.
10/21/85

NDA 19-435

June 17, 1987

Clinical Review of Final Printed Labeling

Date of Submission: April 25, 1986

Sponsor: Burroughs Wellcome Co.
Research Triangle Park, N.C.

Drug: Nix (permethrin) Creme Rinse

Reason for Submission: In our approval letter of March 31, 1986, a number of labeling changes were requested prior to initiation of marketing of the drug. This submission consists of FPL which implements the requested changes.

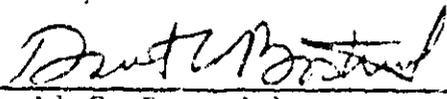
Material Reviewed

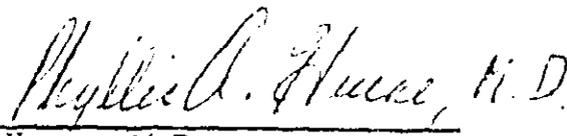
We have compared the FDA requests to the submitted labeling and find that the revised labeling contains the requested changes and is satisfactory.

A call was made to Burroughs Wellcome management to determine the status of the absorption study which was requested in the approval letter. (A determination was to be made of the amount of permethrin absorbed after a single application of the drug). We were informed that the study has been completed and the results will be submitted "within a month."

Finally, we have received a memorandum from the Division of OTC Drug Evaluation which recommends that "hypersensitivity to ragweed" be added to the Contraindications for this drug [REDACTED]. The OTC monograph for pediculicides proposes the following statement under "Warnings": "Use with caution on persons allergic to ragweed." We do not feel that there are sufficient data available to justify ragweed allergy as a contraindication to use of Nix. No adverse reactions of this type was noted in clinical trials or during subsequent marketing. The labeling for this product is adequate as submitted April 25, 1986.

Recommendation: None at this time.


David C. Bostwick


P. A. Huene, M.D.

cc"
Orig NDA
HFN-815; HFN-210
HFN-340 *LO 7/1/87*
HFN-815/PAHuene
HFN-815/DBostwick:js/6/18/87
2500m *C.C.E. 7/1/87*

CHEM REV'S

Division of Anti-Infective
Drug Products
Chemist's Review
Date Completed: 5/10/85

A.1. NDA 19-435

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

2. Product Names:

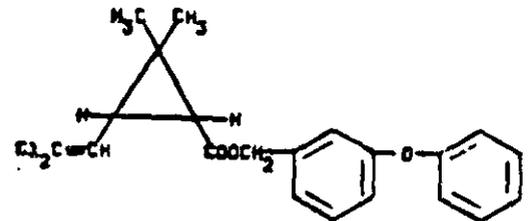
Non-proprietary: permethrin, cis: trans(25:75)

3. Dosage Form & Route of Administration: Rx, Creme rinse for hair

4. Pharmacological Category and/or Principal Indication: Topical pediculicide and ovicide.

5. Structural Formula and Chemical Name(s):

Permethrin 25/75 consists of a mixture of the cis- and trans-isomers of 3-phenoxybenzyl-2', 2'-dimethyl-3'-(2', 2'-dichlorovinyl) cyclopropane-1'-carboxylate in a nominal ratio of 25:75.



B. 1. Initial Submission: 2/28/85

C. Remarks:

D. Conclusions and/or Recommendations:

Lola G. Wayland
Lola G. Wayland

cc: Orig. NDA

HFN-815

HFN-815/CSO

HFN-815/Wayland: gm 5/20/85

R/D Init. by: ARCasola 5/17/85

HFN-815/MO

4043b

ARC 5/23/85

Division of Anti-Infective
Drug Products
Chemist's Review
Date Completed: 7/19/85

A.1. NDA 19-435

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

2. Product Names:

Non-proprietary: permethrin, cis: trans (25:75)

3. Dosage Form & Route of Administration: Rx, Cream rinse for hair

4. Pharmacological Category and/or Principal Indication: Topical
pediculicide and ovice

5. Structural Formula and Chemical Name(s):

B. 1. Initial Submission: 2/28/85

2. Amendments: ()

C. Remarks:

Most deficiencies noted in Chemist's Review () have been satisfactorily addressed. Questions relating to labeling have now been resolved. (21 CFR 201.10(2)).

Method validations have not been completed.

D. Conclusions and/or Recommendations:

Method validation results have not been received. No action is indicated until they are received.

Lola G. Wayland
Lola G. Wayland

cc: Orig. NDA
HFN-815
R/D Init. by: ARCasola 8/29/85
HFN-815/MO
0073c

HFN-815/CSO

HFN-815/Wayland: gm 8/29/85

ARC 8/30/85

Division of Anti-Infective
Drug Products
Chemist's Review
Date Completed: 9/23/85

A.1. NDA 19-435

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

2. Product Names:

Non-proprietary: permethrin, cis: trans (25:75)

3. Dosage Form & Route of Administration: Rx, Cream rinse for hair

4. Pharmacological Category and/or Principal Indication: Topical
pediculicide and ovice

5. Structural Formula and Chemical Name(s):

B. 1. Initial Submission: 2/28/85

2. Amendments: ()

C. Remarks:

Method validation results have been received from Atlanta District (sent 8-1-85; rec'd by me 9-19-85) and the Division of Drug Chemistry. Minor difficulties were experienced with the NDS, partly because not all degradation products could be obtained. Results of testing the drug product are satisfactory and are consistent with results reported by the manufacturer. The assay method for permethrin in the creme rinse is suitable to serve as a regulatory method.

D. Conclusions and/or Recommendations:

Method validation results are satisfactory. The NDA submission is now approvable from the manufacturing and controls standpoint.

Lola G. Wayland
Lola G. Wayland

cc: Orig. NDA

~~HFN-815~~

HFN-815/CSO

HFN-815/Wayland: gm 9/24/85

R/D Init. by: ARCasola 9/24/85

ARC 9/30/85

HFN-815/MO

0092c

PHARM REV'S

(1)

C.S.O.

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-435 (Original Submission, dated 2/28/85)

Date Received: 3/5/85

2-(C)

Date Review Completed: 7/22/85

Applicant: Burroughs Welcome Co.; Research Triangle Park, NC

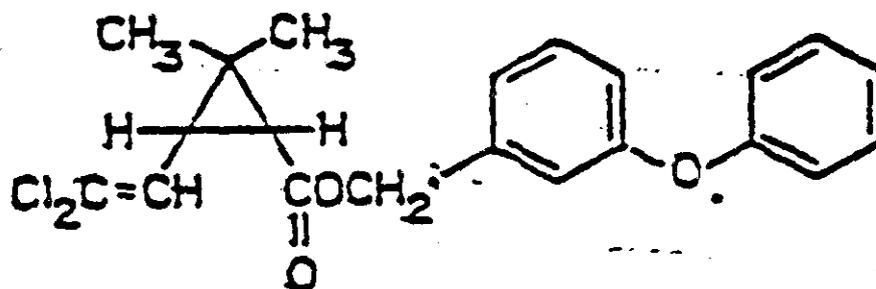
Drug: Permethrin Creme Rinse, 1%

Alternate Name: 21273

Category: Pediculicide [Eradication of Pediculus humanus capitis (head lice)]

Related Submissions: ()

Chemistry:



Composition:

Clinical Indications: Permethrin Creme Rinse 1% is proposed for single-application treatment of infestation with Pediculus humanus var. capitis (head lice) and its eggs. Retreatment may be required for less than 1% of the patients. The labeling recommends that the drug be applied for 10 min. after the hair is shampooed & dried, then allowed to remain on for 10 min. before being rinsed off with water.

Previous Pharmacology Reviews:

List of Preclinical StudiesLabs Performing Studies:

[A] = Wellcome Research Laboratories, Research Triangle Park, NC
 [R] = T.P.S. Inc, Mt. Vernon, Indiana
 [C] = Wellcome Research Laboratories (Berkhamsed), U.K.
 [D] = " " " " (Beckenham), " "

* = Lab indicated under "Title".
 # = Foreign Studies

<u>Lab</u>	<u>Ref.</u>	<u>Document #</u>	<u>Title</u>	<u>Volume</u>	<u>Page</u>
[A]	48	TZZZ/82/0024	Everitt, B.J. (1982). The general pharmacology of BW 21273 <u>Pharmacology - Metabolism</u>	1.3	105
[A]	52	TYHK/83/0003	Allsup, T.L. & Hubbell, J.P. (1983). The percutaneous absorption of permethrin following application of dermal formulations to male rats <u>Snodgrass, H.L. & Nelson, D.C. Dermal penetration & distribution of ¹⁴C-labeled permethrin isomers (Study # 75-51-0351-83)</u> *U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD		134
*	53				181
[B]	57	TTEP/82/0130	Acute Oral Toxicity Study of 1% Permethrin Creme Rinse in the Rat	1.4	1
[B]	58	TTEP/82/0127	Acute Dermal Toxicity Study of 1% Permethrin Creme Rinse in the Rabbit		22
[B]	59	TTEP/82/0128	Acute Eye Irritation Test of 1% Permethrin Creme Rinse in the Rabbit		46
[B]	60	TTEP/82/0129	Acute Skin Irritation Study of 1% Permethrin Creme Rinse in the Rabbit		77
[B]	61	TTEP/82/0126	Sensitization Study of 1% Permethrin Creme Rinse in the Guinea Pig		108
# [C]	62	HEFG 75-4	21273 (25/75) Effect of Different Solvents on the Rat Oral Toxicity		150

<u>Lab</u>	<u>Ref.</u>	<u>Document #</u>	<u>Title</u>	<u>Volume</u>	<u>Page</u>
# [C]	63	HEFG 75-8	21Z73 (25/75) Acute Toxicity Studies by Various Routes of Administration in the Rat, Mouse & Chick		159
# [C]	64	HEFG 77-7	21Z73 - Dermal Toxicity in the Male Rat		175
# [C]	65	HEFG 77-5	21Z73 - Dermal Toxicity in the Female Rat		180
# [C]	66	HEFG 74-6	Ocular Irritancy of 21Z73 in Rabbits		183
# [C]	67	HEFG 74-3	Guinea Pig Sensitization Study with 21Z73 Using the "Maximization" Test Method		186
# [C]	68	HEFG 74-10	Ten-Day Cumulative Oral Toxicity with 21Z73 in Rats		190
# [C]	69	HEFG 74-9	Ten-Day Cumulative Oral Toxicity with 21Z73 in Mice		208
# [C] [D]	70	HEFG 76-1	21Z73, Rat Oral 90-Day Study		215
# [C]	71	HEFG 78-14	Permethrin Oral Administration to Dogs for Six Months	1.5	1
# [D]	72	BPAT 74/19	Fetal Toxicity Study of BW 21Z73 (NRDC 143) in the Rabbit		89
# [D]	73	BPAT 74/10	Fetal Toxicity Study of 21Z73 (NRDC 143) in the Rat		111
# [D]	74	BPAT 74/12	Fetal Toxicity Study of 21Z73 (NRDC 143) in the Mouse		136
# [D]	75	BPAT 79/3	Multigeneration Reproduction Study of 21Z73 (Permethrin) in the Rat		160
[A]	76	TTEP/77/0001	Mutagenicity of BW 21Z73 in L5178 Y/TK ⁺ - Mouse Lymphoma Cells With and Without Exogenous Metabolic Activation		318

Lab	Ref.	Document #	Title	Volume	Page
# [B]	77	HEFG 75-10	21773, Dominant Lethal Study in Male Mice		
[B]	78	HEFG 77-C3	Preliminary Investigation of the Neurological Effects in Rats Offered Diets Containing NRDC 143		335
# *	79	HEFG 80-33	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for 104 Weeks *Life Science Research, Stock, Essex, England		345
# [C]	80	HEFG 81-C044	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks; Addendum to Final Report (HEFG 80-33)	1.6	7
# [C]	81	HEFG 81-C045	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks; Summary Tables of Tissues Examined & Occurrence of Neoplasms; Addendum to Final Report (HEFG 80-33)	1.9	1
# [C]	82	HEFG 81-54	Potential Toxicity & Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks; Justification of Exact Number of Tissues Investigated; Addendum to Final Report (HEFG 80-33)	1.12	356
# [C]	83	HEFG 80-29	Carcinogenicity Study in Mice with Permethrin (BW 21773)		363
# [C]	84	HEFG 81-C049	Potential Toxicity & Oncogenicity in Dietary Administration to Mice; Addendum to Final Report (HEFG 80-29)	1.13	1
[A]	85	TTDR/81/003	Additional Historical Data on Incidence of Mouse Pulmonary Lung Adenoma, and Statistical Analysis of the Incidence of Lung Tumor in Female Mice Treated with Permethrin	1.15	1
*	85A		Permethrin. Assessment of Chronic & Oncogenic Effects: A Summary *Tox. Branch, Hazard Eval. Div., Office of Pesticide Programs, EPA (See my review of Report by EPA.)	1.19	424
					441

"a. Purpose. The insecticide permethrin has been proposed as an impregnant in military fatigue uniforms. Formulations contain varying cis-trans isomer mixtures of the chemical. The potential for skin penetration and bodily distribution of individual isomers and a 50/50 mixture was assessed in dogs and rabbits using the radiolabeled chemicals.

b. Essential Findings/Conclusions. Absorption of topically applied permethrin isomers as measured in excreta through 7 or 14 days registered 30 percent in rabbits and 10 percent in dogs. Urinary excretion was the primary elimination pathway accounting for nearly 75 percent of radioactivity appearing in excreta, usually within the first 24 hours. Radiocarbon recovered in feces was consistently higher (2.5 X) following cis permethrin application than for trans. Absorption/elimination kinetics for the cis-trans mixture generally fell between values observed for the individual isomers. No affinity for tissue binding of permethrin moieties was observed in either animal model. Based on the current and earlier tests, absorption of permethrin in man should be less than 8 percent of the applied dose. The projected bioavailability to man from permethrin impregnated fabric (0.125 mg/cm²) should be less than 0.026 mg/kg/day.

c. Recommendations. It is recommended that permethrin be approved for further testing as a clothing or fabric impregnant at concentrations to 0.125 mg/cm² and that the trans isomer significantly predominate in commercial formulations."

Reference No. 85:

Additional Historical Data on Incidence of Mouse Pulmonary Lung Adenoma:
Historical control data concerning mouse pulmonary lung adenoma was submitted in response to a critique by EPA. This comprised the incidence in controls from 11 carcinogenicity bioassays. After statistical analysis, the applicant reconfirmed his initial conclusion re: the B.W. mouse study (discussed below).

Table 1

B.W. Mouse Study

Incidence of Lung Tumors in F Mice (CFLP) Treated with Permethrin

<u>Dose Tested</u> <u>mg/kg/day</u>	<u>No. of Lung TBA/No. Examined</u>	<u>Percent Incidence</u>
0	3/96	3.1
10	5/71	7.0
50	7/74	9.5
250	15/73	20.6

*Lung tumor-bearing animals

The table below gives the incidence of lung tumors in untreated female CFLP mice from 11 studies, in which the number of lung TBA is known and documented.

Table 2

<u>Study</u>	<u>No. of TBA/No. Examined</u>	<u>Percent Incidence</u>
AA	5/40	12.5
AB	11/58	19.0
AC	6/40	15.0
AD	7/37	18.9
AE	15/50	30.0
AF	3/29	10.3
AG	9/38	23.7
AH	6/40	15.0
AI	9/48	18.8
AJ	12/50	24.0
<u>AK</u>	<u>7/39</u>	<u>17.9</u>
TOTAL	90/469	Mean = 19.2

The applicant pointed out that the control value (3.1%) in the B.W. mouse study was quite low compared to the historical values (range of 12.5-30%) and that the mean % of lung TBA in historical controls (19.2%) is about equal to that of the HD treated group (20.6%). Furthermore, statistical analysis showed no significant findings and it was concluded that permethrin was not oncogenic in mice in the B.W. study.

Reference No. 85A

Permethrin. Assessment of Chronic & Oncogenic Effects:

Introduction: The applicant submitted 7 chronic oncogenicity feeding studies to EPA in support of requests to register food and other uses of permethrin. The following comprises a summary of the EPA report.

Table 3

List of Studies Submitted to EPA

Study	Animals (No/Sex/Group)	Duration (Weeks)	Dosage Levels (Nominal ppm)
A. Mouse:			
1. ICI	70	98	0, 250, 1000, 2500
2. FMC-I	75	104	0, 20, 500, 4000
3. FMC-II	75 M F	104	0, 20, 500, 2000 0, 20, 2500, 5000
* * 4. B-W	100 75	92	0 10, 50, 250*
B. Rat:			
1. ICI	60	104	0, 500, 1000, 2500
2. FMC	60	104	0, 20, 100, 500
* * 3. B-W	60	104	0, 10, 50, 250*

Note: Test material was 40:60 cis:trans isomer in all studies except the B.W. studies (25:75).

*mg/kg/day M = males; F = females

(a) **#4 (mouse) = Ref. 83 - HEFG 80-29; #3. (rat) = Ref. 79 - HEFG 80-33. Both were previously reviewed.

(b) The remaining (3 mouse & 2 rat) studies were not submitted in this NDA nor in the parent IND's; the reason for this omission was not accounted for by the applicant.

(c) Since EPA had to integrate all the data to arrive at a final conclusion, references 83 & 79 will also be described below with the other studies (as reviewed by EPA).

Labs Performing Studies: To be designated as in the above EPA Table.

Mouse:

- | | |
|-----------|--|
| 1. ICI | Central Toxicology Laboratory, ICI |
| 2. FMC-I* | Not disclosed or reviewed (see below). |
| 3. FMC-II | Bio/Dynamics, Inc. |
| 4. B-W | Applicant |

Rat:

- | | |
|----------|---|
| 1. ICI | Central Toxicology Laboratory, ICI |
| 2. FMC** | Bio/Dynamics, Inc. (Very limited in usefulness; see below.) |
| 3. B-W | Applicant |

The following is a slightly edited (summarized) version of EPA's review:

* The FMC-I mouse study was flawed by dose level changes in the MD & HD gps and by an animal identification problem. For these reasons, the study was disqualified by EPA.

** The FMC Rat study was judged to be of very limited usefulness with regard to evaluation of lung tissues for tumors. This resulted from a failure to treat lungs from control & test animals in a comparable manner during the preparation of these tissues for microscopic exam.

The remaining 5 studies were judged to be adequate in evaluating the oncogenic effects of Permethrin. Four of these, the exception being the FMC-II Mouse study, were also found to be useful in evaluating the chronic toxicity of the compound.

Abbreviations to be used: PT = permethrin; inc = increase; dec = decrease;
SS = statistically significant

Mouse Studies

1. ICI Mouse Study

Strain & # Animals: Alderly Park mice; 70/sex

Dosage, Route & Duration: 0, 250, 1000, 2500 ppm in the diet for 98 wks
(sacrificed at 26, 52 & 98 wks)

Results: Relevant non-oncogenic effects observed during the study were: inc'd mortality; inc'd liver enzyme (aminopyrine-N-demethylase) & liver wts; eosinophilia of hepatocytes in both M & F at 2500 ppm. Liver changes observed in this study were considered to be related in large measure to the induction of liver microsomal enzyme activity. Minimal liver changes were also observed at 1000 ppm, but not at 250 ppm.

Table 4

Type	Males (ppm)				Females (ppm)			
	0	250	1000	2500	0	250	1000	2500
Adenoma	11/70 (15.7)	6/70 (8.6)	13/70 (18.6)	17/70 (24.3)	11/70 (15.7)	8/70 (11.4)	10/70 (14.3)	15/70 (21.4)
Adenocarcinoma & Adenoma	0	0	0	0	0	1	1	1
Incidence								

Slight inc in lung adenomas in M showed a trend (SS), but pairwise comparison for both sexes did not reach SS. Mean time for tumor development did not suggest a shortening of the latency period by PT.

Conclusions: EPA was not certain that lung neoplasia in this study was drug-related. However, since lung adenomas were encountered in 2 other studies (FMC-II Mouse & B-W Mouse), EPA was cautious about disregarding the effect.

2. FMC-I Mouse Study: Not reviewed by EPA.
3. FMC-II Mouse Study

Strain & # Animals: Charles River CD-1 mice; 75/group

Route & Duration: in the diet; 104 wks

Dosages: 0, 20, 500 & 2000 ppm to M; 0, 20, 2500 & 5000 to F

Relevant Non-oncogenic Effects: Inc'd mortality in M at 2000 ppm; inc'd liver wts in F at 2500 & 5000 ppm; inc'd lung wts in F at 5000 ppm; Histopathologically, "focal areas of alveolar cell proliferation" (inc'd nos. of lung cells) was observed with dose-related incidence in PT-treated F. Multifocal hepatocytomegaly (inc'd liver cell vol.) was observed with inc'd frequency in both sexes at the HD levels and to a lesser extent in the other treated gps. Necrosis of the liver did not follow a dose-related pattern. Hepatocytomegaly was thought to be probably related to enzyme induction (as suggested by the other mouse studies) rather than being a precursor of necrosis (i.e., PT toxicity).

Oncogenic Effects:

- a) Lung: There was an inc'd incidence of bronchioalveolar adenomas (two separate pathology reports) in F, but not in M, compared to controls (Gp 1), as follows:

Group	I	20.0%
	II (LD)	31.6%
	III (MD)	46.7%
	IV (HD)	58.7%

Furthermore, the number of F mice with alveolar cell adenomas, alveolar cell carcinomas & adenomas and/or carcinomas, demonstrated a sig. dose response.

Various methods of statistical analysis led to the following conclusion by EPA: "Administration of dosage levels of 2500 ppm & 5000 ppm of PT to F mice in this study resulted in a sig. dose-related inc'd incidence of alveolar cell neoplasms (adenoma and/or carcinoma). For alveolar cell carcinomas (alone), the data are somewhat less convincing at the dosage level of 2500 ppm, but there is nevertheless clear evidence of a sig. dose-related inc in alveolar cell carcinomas, particularly at 5000 ppm. PT apparently enhanced the normally expected spontaneous lung tumor incidences in the F, only, in this study."

Note: According to EPA, the total data base did not suggest a dec in latency by PT for induction of tumors.

b) Liver: The incidence of M & F with liver neoplasms (hepatomas & hepatocellular carcinomas) was as follows:

Group	I	M (%)	F (%)
	I	30.1	8.1
	II	39.7	9.2
	III	48.6	32.9
	IV	36.2	40.0

The test for homogeneity of the distribution of liver neoplasms in M was marginally sig. at $p = 0.0740$ (one sided test). In F, there was a SS time-adjusted dose-related trend (Peto's Prevalence Method) with $p \sim 5.5 \times 10^{-10}$ for liver adenoma and/or carcinoma. However, the inc in hepatomas, and not hepatocellular carcinomas, accounted for the inc'd incidence in F. The incidence of hepatocellular carcinoma was not dose-related. There was no indication of a dec'd latency period for liver tumors.

An EPA/FDA joint audit of this study and laboratories conducting /analyzing the results of this study showed it to be useful in determining oncogenic, but not chronic, toxicity effects.

4. B.W. Mouse Study

Strain & # Animals: CFLP mice; 100/sex in control gp, 75/sex in test gps

Dose, Route & Duration: 0 (C), 10 (LD), 50 (MD), 250 (HD) mg/kg/day in the diet for 92 weeks

Relevant Non-oncogenic Effects: Inc'd liver wts in M & inc'd kidney wts in F at the HD. Histologically, M & F of the HD gp showed an inc'd incidence of cuboidal/columnar metaplasia of the alveolar epithelium of

the lung (C = 0% for M & F vs. 4.1% in HD-M & 6.8% in HD-F). "Although controversial, this lesion is considered by some pathologists to be a precursor of lung neoplasms in mice."

Oncogenic Effects: There was a dose-related trend in F (but not M) for adenomatous tumors in the lungs, as follows:

F	%
C	3.1
LD	7.0
MD	9.5
HD	20.3

The incidence was, however, still within historical control range (see EPA report, pp. 25-26).

The occurrence of 3 adenocarcinomas in the lungs of 219 PT-treated F in this study was not indicative in the opinion of EPA to be drug-related. EPA concluded that "the inc'd incidence of lung tumors [adenomas] in F mice observed in this study, together with the other supportive evidence observed in this study, to be highly suggestive of a possible oncogenic effect in lungs of F - particularly when considered in relation to the results of the other two oncogenic studies in mice."

Rat Studies

1. ICI Rat Study: The EPA summary (slightly edited) states the following:

Doses of 0 (C), 500 (LD), 1000 (MD) & 2500 (HD) ppm of PT were administered in the diet to Wistar rats (60/sex/group) for 104 weeks; 11 or 12 rats/sex in each dosage group were sacrificed at 52 wks, the remainder at 105 wks. Relevant non-oncogenic effects were: mortality inc'd in M & dec'd in F at the HD; liver wts inc'd in M & F at the MD & HD and in M only at the LD; liver enzyme (aminopyrine-N-demethylase) activity inc'd in M & F at the MD & HD; hepatocyte vacuolization or hypertrophy in M & F at the MD & HD; kidney wts inc'd in all treated M; pituitary wts inc'd in M at the MD & HD. Body tremors were also observed in M & F during the first 3 wks of the study at the HD.

Conclusion: PT was considered to be non-tumorigenic in this study.

2. FMC Rat Study: PT was administered in the diet to Long-Evans rats (60/sex/group) for 104 weeks at dosage levels of 0, 20, 100 & 500 ppm; 10 M & 8 F from the 100 ppm group were killed at 52 wks. The remaining animals were killed at 104 wks.

Relevant Non-oncogenic Effects: Inc'd liver wts for M at 100 & 500 ppm.

Oncogenic Effects: There was an inc'd incidence of adenomas & adenocarcinomas in the lungs of M rats in this study. However, this study was judged by EPA to be of very limited usefulness with regard to evaluation of lung tumors because of serious flaws in histological methodology (for details, see pp. 15-16 of that report).

NDA 19-435

EPA concluded the following: "Evidence" suggests the possibility of an oncogenic effect occurring in the lungs of treated M rats in this study. Sufficient uncertainty regarding the validity of the incidence figures, however, precludes making a scientifically supportable evaluation of the results."

3. B.W. Rat Study: The EPA summary report (slightly edited) states the following:

PT was administered in the diet to Wistar rats (60/sex/gp) for 104 weeks at dosage levels of 0 (C), 10 (LD), 50 (MD) & 250 (HD) mg/kg/day. Relevant non-oncogenic effects observed at the HD were: inc'd mortality in M; inc'd liver wts in M; hepatocyte hypertrophy in M & F; focal disturbances in growth pattern of thyroid follicular cells in M & F. The microscopic liver & thyroid changes were also observed in M & F at the MD.

None of the tumor types observed in this study were considered related to or attributable to the ingestion of PT.

Non-oncogenic NOEL (no effect level) For Mouse Studies

EPA indicated that some of the liver changes noted in all 3 mouse studies were associated with liver microsomal induction (slight inc in liver wts & aminopyrine-N-demethylase activity) and were therefore not considered to be a toxicological manifestation of PT. However, other liver histopathological effects that could be of toxicological significance were used to determine the NOEL (inc in liver wt, multifocal hepatocytomegaly, hepatocytic pigmentation & eosinophilia of hepatocytes).

EPA concluded the following: "...that liver effects were present in the ICI Mouse Study at 1000 ppm (150 mg/kg/day) and higher, and in the B-W Mouse study at 250 mg/kg/day....liver effects were not present in these studies at levels of 250 ppm (37.5 mg/kg/day) & 50 mg/kg/day. The unusual pattern of distribution of multifocal hepatocytomegaly & necrosis of the liver cells in the FMC-II Mouse study (i.e. in control & treated groups) is very difficult to interpret. These effects could be attributable to the general animal health problems observed in this study or, in the case of hepatocytomegaly, to the ingestion of PT. The Toxicology Branch takes the position that the hepatocytomegaly observed in the 2000, 2500 & 5000 ppm (300, 375 & 750 mg/kg/day) level mice is treatment-related. The weight of evidence favors the 50 mg/kg/day level in the B-W Mouse Study as an appropriate mouse non-oncogenic NOEL."

Non-Oncogenic NOEL for Rat Studies

EPA concluded the following: "As with mice, a consistent finding in all 3 rat studies was liver changes known to be associated with induction of the microsomal enzyme system. This induction phenomenon, for reasons already presented, was again not considered to be an adverse or toxicological effect of concern. The other toxic effects [discussed previously] were used to determine a non-oncogenic NOEL for the rat studies. The NOEL for each study was judged to be: FMC Rat Study, 100 ppm or 5 mg/kg/day; ICI Rat Study, < 500

ppm or \leq 25 mg/kg/day; the B-W Rat Study, 10 mg/kg/day. Based on the weight of evidence in all 3 rat studies, the non-oncogenic NOEL for rat is judged to be 5 mg/kg/day."

Overall Assessment of the Oncogenic Potential in Experimental Animals by EPA:

According to the International Agency for Research on Cancer (IARC), "the widely accepted meaning of the term 'chemical carcinogenesis' --- is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found". EPA considers this definition and the following criteria to evaluate oncogenicity [by PT] in experimental animals when multiple oncogenic studies are available.

1. Oncogenicity in different (a) species, (b) strains, (c) sexes and (d) organs
2. Presence of rare neoplasms & numbers of different types of neoplasms in one or more species
3. Increased incidence of malignant neoplasms
4. Decrease in latency (time to tumor discovery)
5. Dose response relationship
6. Mutagenicity tests (See * below.)
7. Spontaneous tumor incidence in untreated animals

For discussion of all of the above, the reader is referred to the EPA report, pages 21-26.

* "A battery of mutagenicity tests has been performed on Permethrin to detect gene mutation, chromosomal aberrations and primary DNA damage. These tests included studies on S. typhimurium and E. coli (with & without activation), mouse lymphoma, dominant lethal, rat cytogenetics, mitotic recombination in yeast, DNA repair in E. coli and B. subtilis and unscheduled DNA synthesis in human fibroblasts. In none of these studies has Permethrin shown a mutagenic potential.

The mechanism of tumor induction by Permethrin apparently does not operate by biological mechanisms which directly involve the genetic integrity of the cell."

For the "Summary & Evaluation of Criteria Data" by EPA, please see copies of pages 27-31 of the EPA report, attached to this review (Appendix I).

Comments on Carcinogenic Studies:

The applicant submitted to FDA actual reports of only 2 carcinogenicity studies (B-W mouse & rat studies; see Pharm. Rev.)

However, they have submitted, in this NDA report, the review of EPA which encompasses the above-mentioned studies and in addition, 5 (3 mouse, 2 rat) other carcinogenicity studies. Based on the data submitted only to FDA, I had concluded that PT was not found to be tumorigenic in either species. Both EPA & I arrived at the same conclusion regarding the B-W rat study. However, EPA does not entirely share my conclusion about the mouse study, although the incidence of lung tumors in the high-dose females was within historical control range (see p. 17 of IND 21,777 review). On page 26 of their review, EPA states the following: "Comparison of the observed lung tumor incidences in the three long-term mouse studies with the historical control incidences for either sex raises the possibility that these tumors may not be directly related to the ingestion of PT, but rather, may be simply an expression of the variability of the spontaneous and naturally occurring incidence of this lesion in mice. This is particularly true for males for which no tumor/dose relationships were found. Toxicology Branch recognizes some merit in this point of view. However, the definite lung tumor-dose relationship found for the females in the FMC-II Mouse Study and the lung tumor-dose related trend for the females in the B-W Mouse study cannot be ignored. Toxicology Branch considers the lung tumor incidences observed in females in these two studies to be supportive of one another." It is therefore apparent that EPA had more mouse data (than FDA) in arriving at the above conclusion, which deserves merit in my opinion.

Evaluation/Overview

Clinical Use: Permethrin Creme Rinse 1% will be used as a pediculicide (single application, retreatment may be required for less than 1% of the patients). Permethrin, the active ingredient, is a synthetic pyrethroid.

Foreign Studies: The majority of the preclinical pharmacology/toxicology studies were performed abroad and are considered pivotal to a conclusion with regard to safety. These included various types of studies, e.g., acute toxicity, subchronic & chronic toxicity, reproduction, mutagenicity & carcinogenicity studies (see list on pages 3-5 of this review).

Overview (highlights) of Preclinical Toxicity Evaluation: In mice & rats treated IP with doses of permethrin (PT) up to 1000 mg/kg, the drug was relatively well-tolerated and the LD50 value in both species was greater

than 1000 mg/kg. In rats treated PO with 1% PT Creme Rinse, the LD₅₀ was greater than 5 g/kg. LD₅₀ values for mice & rats of PT formulated in different vehicles were:

In rabbits, the LD₅₀ of 1% PT Creme Rinse applied dermally under occlusive dressing was greater than 2 g/kg. Rats exposed dermally for 24 hrs to a 40% w/v sol'n of PT in xylene showed no signs of toxicity clinically or at autopsy.

A study was carried out in rats dosed with PT (up to 15 days) at 6000 ppm of various cis-trans isomers (respectively, 25:75, 40:60 & 90:10%) to determine neurological effects. The severity of CNS symptoms (hyperexcitability, body tremors, flat-footed gait) appeared to be directly related to the cis isomer content. Both light & electronmicroscopy of the peripheral & CNS tissues were inconclusive in determining the etiology of the CNS disorders.

The sensitization potential of PT (1% w/v) in corn oil and 0.1% PT Creme Rinse in 0.9% in saline was assessed in dermally treated guinea pigs. PT was not a sensitizing agent in these test systems. Dermal irritation studies with 1% PT Creme Rinse in rabbits (0.5 ml/site, intact/abraded skin) revealed that the test material was only mildly irritating. Applied to the rabbit's eye (0.1 ml of 1% PT Creme Rinse; 0.1 ml of 40% PT w/v in corn oil), PT was nonirritating, and an ocular hazard under normal conditions of use in humans was predicted to be highly unlikely.

PT w/w was formulated in several commercially available lotions (creme rinses) and these were applied once to dogs' hair at 50 g/dog. Samples of hair analyzed during 14 days of the study revealed that formulations containing protein left large conc'ns of PT on hair and that the addition of 20% isopropanol did not necessarily lead to a higher PT conc'n of the hair.

Absorption of topically applied ¹⁴C-permethrin (study performed by U.S. Armed Forces), as measured in excreta up to 7 or 14 days after application, was 30% in rabbits & 10% in dogs. Urinary excretion accounted for 75% of the radioactivity, usually within 24 hrs. Radiocarbon recovered in feces was always higher (2.5x) following cis PT application than for trans. It was estimated that absorption of PT in man should be less than 8% of the applied dose. The projected bioavailability to man from permethrin impregnated fabric (U.S. Army uniforms; 0.125 mg/cm²) would be less than 0.026 mg/kg/day.

Pharmacokinetic studies were carried out in rats dosed IV or dermally (several formulations) with PT. These studies revealed the following:

1. PT and/or its metabolites were extensively absorbed following dermal application.

2. Rat skin was an important site of PT metabolism and possibly conjugation, thereby limiting the systemic availability of the parent compound.
3. Metabolism of PT to the cis and trans DCVA's (trans or CIS - 3 (2,2 - dichlorovinyl)-2, 2-dimethylcyclopropane-carboxylic acid) was not dose-related, with higher doses favoring more DCVA formation.
4. Following application of 1% creme rinse, about 5% of the PT was absorbed into rat skin prior to washing at 10' after application.
5. After dosing with 5% dermal cream, the urinary excretion of the DCVA's tended to be fairly constant for several days and, therefore, the cream appeared to establish a "reservoir" for PT. However, washing 48 hrs after application removed most of the PT remaining in the skin.

In a number of mutagenicity test systems [S. typhimurium, E. coli, mouse lymphoma, dominant lethal, DNA repair in E. coli & B. subtilis, and unscheduled DNA syntheses in human fibroblasts] performed to detect gene mutations, chromosomal aberrations and primary DNA damage, PT was found to be nonmutagenic.

Teratology studies in mice, rats & rabbits at oral dosage levels up to 200 & 400 mg/kg/day of PT showed no potential for the drug to induce teratogenic effects. In a 3-generation reproduction study in rats with PT at dietary levels of up to 180 mg/kg/day, the drug produced no effect on growth, survival or reproductive ability, and there were no drug-related fetotoxic or teratogenic effects noted.

Oral toxicity studies in rats & dogs (3 & 6 months, respectively) revealed that doses up to 187 & 250 mg/kg/day were relatively well tolerated in both species. A higher dose in rats (357 mg/kg/day) caused hypersensitivity, decrease in body wt gain (M), increased liver wts & decreased thyroid wts.

Two carcinogenicity/toxicity studies in rats & mice were performed and submitted to FDA. Rats were dosed with PT at dietary levels of 0, 10, 50 & 250 mg/kg/day for 104 weeks. Drug-related effects of possible toxicological significance were: a higher mortality rate (HD, M); body tremors from week 90 on (HD gp); increases in liver wt (HD, M); dose-related increase in the incidence of periacinar hepatocytic hypertrophy (MD & HD gps) which was classified as work hypertrophy. Mice were dosed with PT at dietary levels of 0, 10, 50 & 250 mg/kg/day for 91 weeks. Drug-related effects of possible toxicological significance were increased kidney & liver wts in the HD group; however, there was no histological correlation. It was concluded that 10 & 60 mg/kg/day in the rat & mouse studies, respectively, were well tolerated.

There was no evidence of an oncogenic effect by PT in the rat study. In mice, there was a higher incidence of benign adenomas of the lung in the HD F compared to all F groups, including controls (statistically significant, $p < 0.01$, compared to control). However, most of the affected animals in all groups bore only a single adenoma and the mean size of tumors in the HD gp was similar to that in controls and other groups. In contrast, the incidence of

lung adenomas was higher in M controls than in the HD M. Also, the incidence of lung tumors in the F HD gp was within the historical control range and that of the F control gp was quite low compared to historical controls. Finally, in F there was no dose-related increase in incidence of malignant tumors or those bearing multiple lung tumors. In view of the aforementioned, it was concluded that this finding can be regarded as due to chance.

Permethrin and its metabolites have been approved by EPA as insecticide residues in or on certain raw agricultural commodities; see Appendix II (attached copy of Fed. Reg., Vol. 47, No. 196, Oct. 13, 1982). EPA evaluated 6 (3 mouse, 3 rat) long-term carcinogenicity studies; 2 of these were submitted to FDA and the EPA review/report on all 6 was also incorporated in this NDA and reviewed.

Based on evaluation of all available studies and numerous consultations/peer reviews, the following was concluded by EPA:

1. A low oncogenic potential was demonstrated in mice. Treated F had a higher tumor incidence than controls in terms of lung adenomas (250, 375, 750 mpk/day), adenocarcinomas (750 mpk/day) and hepatomas (375, 750 mpk/day).
2. There was no evidence of oncogenic potential in rats.
3. The likelihood of oncogenicity in humans is slight.

Recommendations: The following labeling changes are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Statement should be revised to read as follows:

"There is evidence from three separate studies that in the mouse, chronic feeding of permethrin leads to increased incidence of pulmonary adenoma. In one of these studies, there was a dose-related increase in incidence of alveolar cell carcinoma, as well as liver neoplasia in the females. Permethrin does not appear to be oncogenic in the rat, however.

Since permethrin failed to show evidence of mutagenic potential in an extensive battery of in vitro & in vivo genetic toxicity studies, it is likely that the oncogenic activity seen in mice represents an epigenetic phenomenon.

Permethrin did not cause any adverse effect on reproductive function at a dose of 180 mg/kg/day, orally, in a three-generation rat study."

Pregnancy: In the statement proposed by the applicant, insert in the first sentence after "and rabbits", in parentheses, the following:
"(200-400 mg/kg/day, orally)."

cc: Orig. NDA
 HFN-815
 HFN-340
 HFN-815/GCDebbas/smc/8/5/85
 R/d init.by:JMDavitt
 Appendices (2) attached.
 0036p

HFN-815/MO
 CSO

Gamil Debbas
 Gamil C. Debbas, Ph.D.

Supplements

3.1



JUL 27 1988

ADA 19-435/S-001

Mr. Donald A. Knight
Burrroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Knight:

We acknowledge the receipt on January 20, 1988 of your supplemental New Drug Application dated January 14, 1988 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for NIX (permethrin) Creme Rinse 15.

The supplemental application provides for modifications in the synthesis of permethrin, involving primarily a additional distillation of the acid chloride intermediate, to improve its quality.

We have completed our review of this supplemental application and it is approved. Our letter dated March 31, 1986 detailed the conditions relating to the approval of this application.

Sincerely yours,

ARC

Armand R. Casola, Ph.D.
Supervisory Chemist
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA
HFD-520
HFD-520/CSO/Bostwick
HFD-520/ARCasola
HFD-520/HO/Huene
HFD-520/Wayland gm 7/1/88 *JHW 7/1/88*
HFD-520/Gavrilovich
R/D init. by: ARCasola 6/29/88 *ARC 7/8/88*
Approve
1075c





Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N. C. 27709

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel 919 248-3000

January 14, 1988

SPECIAL SUPPLEMENT -- CHANGES BEING EFFECTED

Edward Tabor, M.D., Director
Division of Anti-Infective Drug Products
Office of Biologic Research and Review
Center for Drugs and Biologics
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 19-435 REF. NO. 5661
NDA SUPPL FOR CS

Re: NDA 19-435
NIX™ (Permethrin) 1%
Creme Rinse

Dear Dr. Tabor:

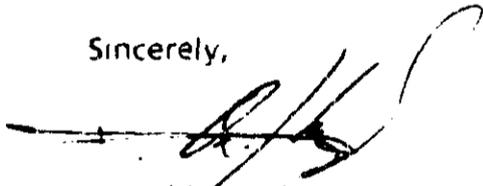
In accordance with CFR 314.70(c)(1), we submit herewith a "Special Supplement - Changes Being Effected" for the subject product to provide for improvements to the synthesis of permethrin manufactured by The Wellcome Foundation, Ltd., Dartford, England.

Specifically, an additional distillation of the acid chloride intermediate produced at Stage 2 of the synthetic process is being performed to improve its quality. Other modifications were made to utilize equipment and facilities in the manufacturing process more efficiently.

Analytical profiles of drug substance included herein produced by the new and former synthetic methods are compared to show that the modified synthetic process results in drug of improved quality.

No change in the regulatory Analytical Standard for Medical Grade Permethrin is required because of these improvements. The additional control provides increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess.

Sincerely,


Donald A. Knight
Associate Director
Drug Regulatory Affairs

DAK/cp*
TRZO/88/0003
Enclosure

RECEIVED
JAN 20 1988
HFM-815
CDB - DAK

NDA SUPPLEMENT REVIEW

CHEMIST'S REVIEW	1. ORGANIZATION DAIDP	2. NDA NUMBER 19-435
3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE) Burroughs Wellcome Co. 3030 Cornwallis Road Research Triangle Park, NC 27709	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER(S) DATE(S)
6. NAME OF DRUG NIX	7. NONPROPRIETARY NAME permethrin	S-001 1/14/88

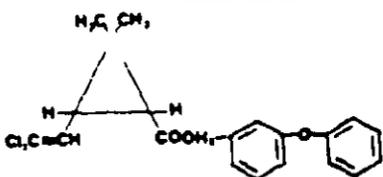
8. SUPPLEMENT(S) PROVIDES FOR: a change in the synthesis of permethrin involving an additional distillation of the acid chloride intermediate to improve its quality.

9. AMENDMENTS AND OTHER (REPORTS, etc) DATES

10. PHARMACOLOGICAL CATEGORY pediculicide	11. HOW DISPENSED X Rx OTC	12. RELATED IND/NDA/DMF(S)
13. DOSAGE FORM(S) creme rinse	14. POTENCY(ies) 1%	

15. CHEMICAL NAME AND STRUCTURE

Permethrin, Medical Grade consists of a mixture of the cis and trans isomers of 1-(phenylbenzyl) 3-(2,2-dimethyl-1-hydroxyethyl)-1-(2,2-dimethyl-1-hydroxyethyl) cyclopropane carboxylate in a nominal ratio of 25:75.



16. RECORDS AND REPORTS

CURRENT	Yes	No
REVIEWED	Yes	No

17. COMMENTS

Several modifications have been made in the synthesis of NDS by the manufacturer (The Wellcome Foundation, Ltd, Dartford, England). They are not substantive changes, acting only to enhance the purity of the acid chloride intermediate in the already approved synthesis. The specifications of the NDS remain unchanged. Comparative data between lots of intermediate produced by both old and new processes show a purer product resulting from the modifications.

Stability data on a lot of drug product using new process NDS show a satisfactory product. The stability studies will continue according to the approved protocol.

18. CONCLUSIONS AND RECOMMENDATIONS:

The supplement is for changes being effected. From the manufacturing and controls standpoint it may be approved.

cc: ORIG NDA
 HFD-520 HFD-520/CSO
 HFD-520/MO HFD-520/Wayland:gm 7/1/88
 R/D initialed by: ARCasola 6/29/88 *ARC 7/8/88*

19. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Lola G. Wayland	<i>Lola G. Wayland</i>	5-28-88
DISTRIBUTION	ORIGINAL JACKET REVIEWER	DIVISION FILE

NDA 19-435/S-002

Mr. Donald A. Knight
Associate Director, Regulatory Affairs
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Knight:

We acknowledge the receipt on March 9, 1988 of your supplemental New Drug Application dated March 9, 1988 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for NIX (permethrin) Creme Rinse 1%.

The supplemental application provides for broadening the limits for preservatives in the drug product from 90-110% to 80-120%, and tightening the impurity limits in the new drug substance.

We have completed the review of this supplemental application and it is approved. Our letter of March 31, 1988 detailed the conditions concerning the approval of this application.

Sincerely yours,

ARC

Armand R. Casola, Ph.D.
Supervisory Chemist
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: cc: Orig NDA

HFD-520

HFD-520/CSO/Bostwick

HFD-520/ARCasola

HFD-520/MO/Huene

HFD-520/Wayland gm 8/30/88 *ARC 8/30/88*

R/D init. by: ARCasola 8/29/88

Approve

135c

ARC 8/31/88

NDA SUPPLEMENT REVIEW

AUG 31

CHEMIST'S REVIEW

1. ORGANIZATION
DAIDP

2. NDA NUMBER
19-435

3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE)
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

4. AF NUMBER

5. SUPPLEMENT(S)
NUMBER(S) DATE(S)
S-002 3/09/88

6. NAME OF DRUG
NIX

7. NONPROPRIETARY NAME
permethrin

8. SUPPLEMENT(S) PROVIDES FOR:
revising the NDS specifications relating to impurities
and broadening the limits for preservatives in the
drug product from 90-110% to 80-120%.

9. AMENDMENTS AND OTHER
(REPORTS, etc) DATES

10. PHARMACOLOGICAL CATEGORY
pediculicide

11. HOW DISPENSED

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM(S)
topical creme rinse

14. POTENCY(ies)
1%

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT	Yes	No
REVIEWED	Yes	No

17. COMMENTS
To support the broadening of the 3 preservatives' limits, data are presented demonstrating preservative effectiveness to microbial challenge at levels representing 25, 50, 75, and 100% of labeled preservative strength. Assay values of all 3 preservatives at each level are presented. Since the data show effectiveness at a level as low as 25% of label, broadening of the specifications from 90-110% to 80-120% is reasonable and still offers a large margin of safety.

COMMENTS CONT. ON NEXT PAGE

18. CONCLUSIONS AND RECOMMENDATIONS:
The supplement may be approved.

cc: cc: Orig NDA
HFD-520
HFD-520/C50/Bostwick
HFD-520/ARCasola
HFD-520/MO/μriene
HFD-520/Wayland gm 8/30/88
R/D init. by: ARCasola 8/29/88 *ARC 8/31/88*

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Lola G. Wayland	<i>Lola G. Wayland</i>	8-26-88
DISTRIBUTION	ORIGINAL JACKET	REVIEWER
		DIVISION FILE



Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N. C. 27709

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

March 9, 1988

Edward Tabor, MD, Director
Division of Anti-Infective Drug Products
Office of Biologic Research and Review
Center for Drugs and Biologics
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 19-435 REF. NO. 5002
NDA SUPPL FOR CR

RE: NDA 19-435
NIX® (Permethrin 1%)
Creme Rinse

Dear Dr. Tabor:

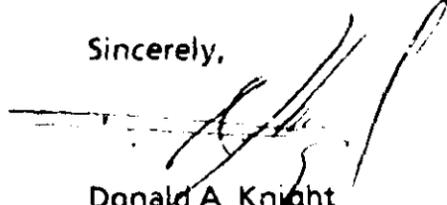
We submit herewith a supplemental application to provide for changes to the analytical methods for NIX Creme Rinse.

We wish to widen the limits for the preservatives contained in the drug product. The limits are being revised from 90% - 110% to 80% - 120%. Preservative efficacy data provided herein support the broader limits.

We also wish to revise the Analytical Standard for the drug substance, Permethrin, Medical Grade. An additional process impurity, 3-phenoxybenzyl 4,6,6-trichloro-3,3 dimethyl-5-hexenoate (PTDH) has been identified, quantitated and specifications included in the Analytical Standard for Permethrin, Medical Grade.

As a result of this impurity being identified, we are proposing to tighten the limits for 2 other related substances and tighten the total permethrin assay limit from 93% to 95%.

Sincerely,


Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
FBI
MAR 11 1988