CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 019918/ S004

Trade Name : NIX CREAM RINSE

Generic Name: Permethrin

Sponsor : Warner Lambert Company

Approval Date: November 1, 1996

BLAY
540

NDA 19-918/S-004

NOV 1 [illegible]

Warner Lambert Company
Attention: Jean Grieve
170 Tabor Road
Morris Plains, NJ 07950

Dear Ms. Grieve:

We acknowledge your May 15, 1991, supplemental new drug application received on May 16, 1991, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nix®(permethrin) Creme Rinse, 1%.

Please refer to your not approvable letter dated June 15, 1992, and your approvable letter dated May 3, 1995.

We acknowledge receipt of your communications dated June 23 and December 28, 1992; March 16, 1993; December 27, 1995; and, September 20, 1996.

This supplemental application provides for the prophylactic use of this product during head lice epidemics.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on September 20, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 19-918. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Dr. Roy Blay, Consumer Safety Officer, at (301) 827-2020.

Sincerely yours,

11/4/96

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure:

cc:
Original NDA 19-918 RB 11/1/96
HFD-540/Div. Files
HFD-540/Blay/Wilkin/Katz/Huene/Jacobs/DeCamp/Mokhtari-Rejali
HFD-2/Lumpkin (with labeling)
HFD-105/Weintraub (with labeling)
DISTRICT OFFICE
HFD-92 (with labeling)
HFD-613/(with labeling)
HFD-735 (with labeling
HFD-222
HF-2/MedWatch (with labeling)
HFD-40/(with Labeling)

Concurrences:
HFD-540/SPM/Kozma-Fornaro/10.24.96
HFD-540/DEP DIR/Katz/10.25.96

drafted: /October 24, 1996/c:\royblay\letters\nda\approval\19918.002
r/d Initials:
final:

APPROVAL

NDA 19-918/S-004

Burroughs Wellcome Co.
Attention: Michael J. Dalton, Pharm.D.
Head, Department of Pharmaceutical Products
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, NC 27709

MAY 3 1995

Dear Mr. Dalton:

Please refer to your May 15, 1991 (S-004) and February 10, 1993 (S-005) supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NIX® (permethrin cream rinse) Cream Rinse.

The supplements provide for a prophylactic use of the product during head lice epidemics (S-004)

We also acknowledge receipt of your March 16, 1993 amendment in response to the June 15, 1992 not approvable letter (S-004).

We have completed the review of these supplemental applications, as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling (FPL) with the revisions identified in the attached draft labeling. The FPL should be identical to the attached draft labeling which was based on your March 16, 1993 submission.

Please submit fifteen copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact Mrs. Regina D. Joyce at 301-594-4109.

Sincerely yours,

5/2/95

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachment

cc: NDA 19-918
HFD-540
HFD-500
District Office
HFD-82
HFD-540/CSO/Turtil
HFD-540/CLIN/Joyce 4/17/95
HFD-540/MO/Chambers 4/17/95

APPROVABLE

NDA 19-918/S-004

JUN 15 1992

J. Greg Perkins, Ph.D.
Head, Department of Consumer Products
Drug Regulatory Affairs
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Dr. Perkins:

Reference is made to your supplemental New Drug Application (NDA) dated May 15, 1991, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nix^{R} (permethrin creme rinse), 1%.

The supplemental New Drug Application provides for the addition in the labeling for the drug product of prophylactic use during head lice epidemics.

We have completed the review of this supplemental New Drug Application and have concluded that the information presented is inadequate and that the supplemental New Drug Application is not approvable at this time.

Under section 505(d) of the Act and 21 CFR 314.125(b)(5) of the implementing regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Nix^{R} (permethrin creme rinse), 1% will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

Specifically, none of the three clinical studies specified in this supplemental New Drug Application employed the treatment regimen recommended in the proposed labeling. Furthermore, in the proposed labeling, the exact number of applications recommended for prophylactic use is uncertain and requires clarification. Therefore, the data submitted did not adequately demonstrate that Nix^{R} (permethrin creme rinse), 1% would be effective in the prevention of infestation or reinfestation or both during epidemics.

We reserve comment on the evaluation of safety associated with the proposed prophylactic use of this drug product until our concerns regarding efficacy are adequately addressed.

Within 10 days after the date of this letter, you are required to amend the supplemental New Drug Application, or notify us of an intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the FDA may proceed to withdraw the supplemental New Drug Application. Any amendment should respond to all the deficiencies listed. A partial response will not be processed as a major amendment, and, therefore, the review clock will not be activated.

Should you have any questions concerning this supplemental New Drug Application, please contact Ms. Maria Rossana R. Cook, Project Manager at 301-443-0335.

Sincerely yours,

MML 6/15/92

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 19-918/S-004
ATL-DO
HFC-130
HFD-82
HFD-500
HFD-638
HFD-735
[redacted]
HFD-520/DIV DIR/Lumpkin
HFD-520/MO/Huene 6/8/92
HFD-520/PHARM SUPV/Osterberg
HFD-520/CHEM/Mokhtari-Rejali
HFD-521/PROJ MGR/Cook

NOT APPROVABLE

MML 6-04-92

Concurrences:

HFD-520/MO SUPV/Alpert 6/15/92
HFD-520/PROJ MGR SUPV/Bona 6/15/92

NOV 25 1996

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 19-918
S-004

November 25, 1996

SPONSOR: Warner Wellcome
Morris Plains, NJ

DRUG: Nix creme rinse 1%

CLINICAL INDICATION: Head lice

DATE OF AMENDMENT: November 13, 1996

REASON FOR AMENDMENT: Revisions in the product labeling.

The sponsor has made some minor revisions in the product labeling. These consist of 1) a statement that the distributor is Warner Lambert, 2) addition of the words before in the DESCRIPTION section, and 3) addition of the words before the listing of the inactive ingredients in the DESCRIPTION section.

Reviewer's comments: These revisions in the labeling are minor and are acceptable.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Blay

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 19-918
S-004

March 11, 1996

SPONSOR: Warner Wellcome
Morris Plains, NJ

DRUG: Nix creme rinse 1%

CLINICAL INDICATION: Head lice

DATE OF AMENDMENT: December 27, 1995

REASON FOR AMENDMENT: Submission of final printed labeling in response to the approvable letter of 5/3/95.

The sponsor has submitted final printed labeling in the amendment of 12/27/95. This is in accordance with the approvable letter of May 3, 1995, with, however, one exception. The sponsor has not complied with the requested addition of the qualifying phrase 'for 14 days' to the statement 'prevents reinfestation' on the front box label. The 14 day qualification on the claim for prevention of reinfestation is presented elsewhere in the product labeling, as was requested.

The sponsor feels that the consumer would not be able to discriminate between Nix and a competitor monographed product which bears a claim for prevention of reinfestation but does not qualify the reinfestation prevention time.

Reviewer's comments: The data do not support a claim for prevention of reinfestation for longer than 14 days. The sponsor should therefore qualify this claim by the statement 'for 14 days' or omit the claim for prevention of reinfestation entirely.

No allowable claims for prevention of reinfestation were found in the monograph for OTC pediculicide products. Michael Benson of HFD-560 was consulted in this regard, and he agreed that such a claim was not included in the monograph. The sponsor's contention that the recommended statement would place them at a competitive disadvantage is therefore not valid.

It is recommended that this amendment not be approved.

cc: Orig NDA 19-918
HFD-540
HFD-540/MO/PHuene
HFD-540/Pharm/Jacobs
HFD-540/Chem/DeCamp
HFD-540/CSO/Cross

Phyllis A. Hueñe, M.D.

3/26/96
3/31/96

Phyllis A. Hueñe, M.D.

MAR 9 1995

Supervisory Medical Officer's Review of NDA 19-918
Supplement 4

NDA #19-918
SMO Review #1

Submission: 3/16/93
Review completed: 2/19/95

Trade name:	NIX® Creme Rinse
Generic name:	Permethrin creme rinse
Sponsor:	Burroughs Wellcome Co.
Therapeutic Category:	Pediculicide
Proposed Indication(s):	For the treatment of head lice and for prophylactic use during head lice epidemics
Dosage Form(s) Route(s) of Administration:	Topical creme rinse

Related Reviews:
MOR of NDA 19-435 dated 10/2/85 Permethrin Creme Rinse - Rx
MOR of NDA 19-918/S04 dated 12/9/91 Permethrin Creme Rinse - OTC
MOR of NDA 19-918/S04 Amendment dated 4/12/93

Background:

Supplement 4 to NDA 19-918 provides for the addition in the labeling for prophylactic use during head lice epidemics. The supplement received a not approvable letter on 6/15/92 because the clinical trials submitted in the supplemental application did not employ the treatment regimen recommended in the proposed labeling (3 applications at 2 week intervals). The applicant in their 12/28/92 and 3/16/93 amendments has responded to the not approvable letter by changing the recommended treatment regimen to one that was studied in the clinical trials. In an interoffice memorandum, the Director of the Division of Anti-Infective Drug Products raised a series of questions concerning the studies used to support an approval of this supplement. While unusual, the reviewing Medical Officer had used some of the studies submitted to the original NDA for NIX (NDA 19-435) as the basis of approval for the supplement. This review while not re-reviewing each of the studies in detail will list for clarification the studies previously submitted to the two relevant NDAs.

Labeling recommendations have also been included.

Study Number	Investigators	Design	Test Products	Dosing	Free of Lice Day 7	Free of Lice Day 14
#1* Study 1 N 19-435	Taplin Castillero	Double blind Parallel 1 open label arm - Kwell	Nix 1% Vehicle Kwell	1 application	Nix 29/29 (100%) Vehicle 3/34 (9%) Kwell 20/30 (67%)	Nix 28/29 (97%) Vehicle 2/34 (6%) Kwell 13/30 (43%)
#2** Study 2 N 19-435	DiNapoli Orthoefer Parish Wagner Englander Brandenburg Deinard	Single blind Parallel	Nix 1% Kwell	1 application for patients 1 application for members of household	**Patients** Nix 148/149 (99%) Kwell 133/143 (93%) **Family Members** Nix 111/111 (100%) Kwell 95/105 (90%)	**Patients** Nix 148/149 (99%) Kwell 121/143 (85%) **Family Members** Nix 109/111 (98%) Kwell 94/109 (86%)
Study Number	**Investigators**	**Design**	**Test Products**	**Dosing**	**% Reinfested**	**Median time to reinfestation**
#3 08-01 N 19-918	Taplin Castillero	Single blind Parallel	Nix Nix Prell	1 application of Nix 8 weekly applications of Nix 8 weekly applications of Prell	1 Application Nix 26/29 8 Weekly Appl Nix 1/30 8 Weekly Appl Prell 27/29	Nix x1 4.7 weeks Nix x8 >9 weeks Prell x8 1.1 weeks
#4 17-01 N 19-918	Taplin Castillero	Single blind Parallel	Nix Rid R&C	1 application	Nix 2/32 at 2 wks - 29/32 total Rid 23/33 at 2 wks - 33/33 total R&C 29/33 at 2 wks - 33/33 total	Nix 4.4 weeks Rid 1.1 weeks R&C 0.7 weeks
#5 11-01 N 19-918	Clore, Smith, Beal,Wagner, Orthoefer, DiNapoli Bowerman	Double blind Parallel	Nix Vehicle	8 Weekly applications	Population in this study were not infested with head lice.	

*#1

	Mean hatch rates Nits obtained prior to treatment	**Mean hatch rates** Nits obtained after treatment
Permethrin	>90%	30%
Vehicle	>90%	86%
Kwell	>90%	55%

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.

**#2

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

Reviewer's Comments:

I concur with the Medical Officer's assessment that Nix Creme Rinse has been shown to protect greater than 95% of patients against infestation for at least two weeks in the submitted studies. A second prophylactic application may be recommended two weeks after the first because the life cycle of a head louse is approximately four weeks and a second application is likely to provide continued protection during an epidemic. The additional safety information collected from the eight weekly applications supports the two applications.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

APPEARS THIS WAY

Division Director's First Memo Questions

[See also May 6, 1993 answers prepared by Dr. Huene. The answers listed below are consistent with those answers, but include additional information for clarification.]

Q2. WHERE DID THE "FOR FAMILY MEMBERS" COME FROM IN THE MOST RECENT PROPOSED LABEL?

Reviewer's Comments:

Study #2 in the original NDA [19-435] treated both "index cases" and "members of the household." The applicant has proposed the language "for family members" although "members of the household" may be more appropriate.

Q3. WHERE DOES THE 20% FOR THE INSTITUTIONALIZED PEOPLE COME FROM?

Reviewer's Comments:

This is an arbitrary definition of an epidemic. However, after a review of the literature: Slonka et al published a paper "An epidemic of pediculosis capitis" [J Parasitol. 1977 Apr; 63(2):377-83] in which a city wide prevalence survey showed 7.2% of all pupils infected and particular sub-groups showed rates of 20%; Magra-Saenz-de-Buruaga-G et al published a paper showing a preschool and elementary prevalence of 9.4% (range 1.8% to 31.6%) [Rev Sanid Hig Publica Madr 1989 Jan-Feb; 63(1-2): 49-62.] There are also reports of prevalence ranging from 75%-100% in schools in Bangladesh [Clin Ther 1994 Jan-Feb; 16(1) 57-64].

A 20% prevalence rate at an institution seems appropriate for a definition of an epidemic of pediculosis capitis.

Q4. THE >95% CLAIM SEEMS TO BE BASED ONLY ON THE ONE PANAMANIAN STUDY WHERE 30/32 (94%) PEOPLE WERE KEPT FREE OF INFESTATION FOR 2 WEEKS. THIS IS ONLY ONE STUDY AND VERY SMALL (ALBEIT SIGNIFICANT) NUMBERS. DO WE REALLY WANT THIS NUMERICAL CLAIM BASED ON AN UNCORROBORATED STUDY?

Reviewer's Comments:

The >95% claim is based on the original studies submitted to NDA 19-435. These studies show replicated results by different investigators at >97%. There is however, a report of a Chinese study [Kao Hsiung I Hsueh Ko Hsueh Tsa Chih. 1992 May; 8(5): 255-65] which describes a comparative clinic trial with Nix. The cure rate of Nix in this study is 81%, but it was the highest cure rate of any of the four treatments used. The authors attributed the low cure rates to be possibly due to the fact that many school girls have long hair.

It may be more reasonable to provide a cure range of 80-99%, but the >95% claim is currently true for U.S. studies.

Q5. IF THE PROPHYLAXIS CLAIM IS NOT YET PART OF THE PROFESSIONAL LABEL, IT SEEMS WE HAVE THE TWO PANAMANIAN STUDIES WITH SURROGATE TYPE SITUATIONS UPON WHICH TO BASE THIS CLAIM; HOWEVER, THEY ARE BOTH BY THE SAME INVESTIGATORS. DO SUSAN AND PHYLLIS [MEDICAL OFFICERS] NOT THINK THIS PROBLEMATIC?

Reviewer's Comments:

As identified in this review, the conclusions are based on both a domestic study and the Panamanian studies.

Division Director's Second Memo Questions:

QQ1. ON WHAT BASIS WOULD WE PUT STATEMENTS ABOUT "FOR FAMILY MEMBERS" AND "EPIDEMICS AT INSTITUTIONS WHERE GREATER THAN 20% OF THE PEOPLE ARE INFESTED" IN THE LABEL? THERE IS NO DATA OR RATIONAL EXPLANATION IN THE NDA THAT I HAVE SEEN.

Reviewer's Comments:

See revised answers to Questions Q2 and Q3 above. Members of the same household have been studied. The numerical definition of an epidemic is meant to limit use to situations which are clearly believed to be epidemics (i.e., above typical prevalence rates of 10%).

QQ2. THE >95% CLAIMS SEEMS TO BE BASED ONLY ON THE ONE PANAMANIAN TRIAL. SUCH SPECIFICS SHOULD BE CORROBORATED IN SOME WAY, DON'T YOU THINK?

Reviewer's Comments:

See revised answer to Question Q4 above.

QQ3. WHERE IS THE CORROBORATION OF THE PANAMANIAN EXPERIENCE? PHYLLIS REFERRED ME TO TWO TRIALS IN THE ORIGINAL NDA; HOWEVER, I UNDERSTOOD THOSE TO BE TREATMENT TRIALS AND NOT PROPHYLAXIS TRIALS. THEY SEEM TO PROVIDE LITTLE SUPPORT TO THE NEW CLAIM. 08-01 AND 17-01 ARE BOTH PERFORMED BY THE SAME INVESTIGATORS, SO I HAVE RESERVATIONS ABOUT COUNTING THEM AS "CORROBORATIVE." SUCH IS NOT OUR USUAL STANDARD. 11-01 IS THE LARGE US STUDY WHICH (1) IS PERFORMED USING A DOSING REGIMEN THAT IS NOT THAT REQUESTED IN THE PROPOSED LABEL AND (2) DEMONSTRATES THAT CASUAL PROPHYLACTIC USE DOES NOT BEAT VEHICLE IN A US POPULATION - INTERESTINGLY, THE ONLY INFESTED CHILDREN IN THIS TRIAL HAPPEN TO BE THOSE IN THE TREATMENT ARM.

I GUESS I STILL DON'T UNDERSTAND WHERE THE RECOMMENDATION FOR APPROVAL IS COMING FROM?

Reviewer's Comments:

Study 11-01 is a flawed study because the patients enrolled did not have pediculosis capitis and were not necessarily household contacts of individuals with pediculosis. The only value of study 11-01 is as a safety study, supporting the safety of multiple applications (as frequently as once per week).

The approval recommendation is based on the results of all five studies, although primarily on the two studies which supported the original approval. The labeling states that retreatment is not usually necessary, but that a second treatment can be given if live lice are observed seven days or more after the first application. The benefit of each application is only intended to support 14 days of prophylaxis.

APPEARS THIS WAY
ON ORIGINAL

6 Pages (8-13)
Deleted
Professional Labeling

Conclusions/Recommendations:

Supplement 004 to NDA 19-918 is recommended for approval provided labeling revisions listed in this review are completed.

Wiley A. Chambers, M.D.
Supervisory Medical Officer

cc: HFD-540
HFD-340
HFD-540/CSO/Cook
HFD-540/CHEM/Mokhtari-Rejali
HFD-520/MICRO/Sheldon
HFD-540/PHARM/Jacobs
HFD-540/MO/Huene
HFD-540/SMO/Chambers

3/9/95

MAR 3 1995

Supervisory Medical Officer's Review of NDA 19-918
Supplement 5

NDA #19-918/S-05
SMO Review #1

Submission: 3/16/93
Review completed: 2/20/95

Trade name:	NIX® Creme Rinse
Generic name:	Permethrin creme rinse
Sponsor:	Burroughs Wellcome Co.
Therapeutic Category:	Pediculicide
Proposed Indication(s):	For the treatment of head lice and for prophylactic use during head lice epidemics
Dosage Form(s) Route(s) of Administration:	Topical creme rinse

Related Reviews:
MOR of NDA 19-435 dated 10/2/85 Permethrin Creme Rinse - Rx
MOR of NDA 19-918/S04 dated 12/9/91 Permethrin Creme Rinse - OTC
MOR of NDA 19-918/S04 Amendment dated 4/12/93
SMOR of NDA 19-918/S04 dated 2/19/95

Background:

Recommendations from the Medical Officer and Supervisory Medical Officer Reviews have been included in this review.

Labeling recommendations have also been included.

3 Pages (2-4)
Deleted - Draft
Labeling

Conclusions/Recommendations:

NDA 19-918 is recommended for approval provided labeling revisions listed in this review are completed.

Wiley A. Chambers MD
Wiley A. Chambers, M.D.
Supervisory Medical Officer

cc: HFD-540
HFD-340
HFD-540/CSO/Cook
HFD-540/CHEM/Mokhtari-Rejali
HFD-520/MICRO/Sheldon
HFD-540/PHARM/Jacobs
HFD-540/MO/Huene
HFD-540/SMO/Chambers

3/5/95

5.1 APR 13 1993

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT AMENDMENT TO NDA 19-918
S-004

April 12, 1993

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

DRUG: Nix (permethrin) creme rinse

INDICATION: Head lice

DATE OF SUPPLEMENT: May 15, 1991

DATE OF AMENDMENTS: December 28, 1992 and March 16, 1993

APPROVED INDICATION: Treatment of pediculosis capitis (single application).

REASON FOR SUPPLEMENT: New indication being sought - prophylaxis of head lice infestation during head lice epidemics.

PROPOSED TREATMENT REGIMEN: A second application two weeks after the first application is recommended for prophylaxis.

APPEARS THIS WAY
ON ORIGINAL

The December 28, 1992 amendment to the above supplement is in response to our non-approvable letter of June 15, 1992, and provides revised labeling which was felt by the sponsor to address the issues raised in the letter. In subsequent telephone conversations between the sponsor's representatives and Dr. Susan Alpert, Ms. Rosemary Cook, and myself, further revisions in the 'Prophylaxis' section of the labeling were agreed upon. It was felt that these revisions would serve to clarify the number of applications recommended for prophylaxis during epidemics, and to modify the directions for such use so as to be in accordance with the treatment regimens employed in the clinical studies.

The amendment of March 16, 1993, provides the further labeling revisions. The entire section entitled 'Prophylactic Use' in the original supplement has been deleted, and a new section entitled 'Prophylaxis' has been added, which reads as follows.

"Prophylaxis

The method of application of Nix Creme Rinse for prophylaxis is identical to that described above for treatment of a lice infestation except nit removal is not required.

Directions for use

One application of Nix Creme Rinse has been shown to protect greater than 95% of patients against infestation for at least two weeks. A second prophylactic application is highly recommended two weeks after the first. Because the life cycle of a head louse is approximately four weeks, a second application ensures continued protection during an epidemic."

Evaluation: The revised labeling of March 16, 1993, is felt to adequately address the issues in the non-approvable letter of June 15, 1992.

Recommendations: It is recommended that the supplemental application, which provides revised labeling for the prophylaxis of head lice infestation during epidemics, be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

4/13/93

cc: Orig. NDA
HFD-340
HFD-520
HFD-520/MO/PHuene
HFD-520/Pharm/Osterberg
HFD-520/Chem/DeCamp
HFD-520/CSO/RCook

N19918.S4A

APR 30

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT TO NDA 19-918
S-004

December 9, 1991

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

DRUG: Nix (permethrin) cream rinse 1%

APPROVED INDICATION: Treatment of pediculosis capitis (single application).

REASON FOR SUPPLEMENT: New indication being sought - prophylaxis of head lice infestation during head lice epidemics.

PROPOSED TREATMENT REGIMEN: One application every two weeks for a four week period (three applications).

DATE OF SUBMISSION: May 15, 1991

RELATED SUBMISSIONS: Approved NDA 19-435 for Nix cream rinse in the treatment of pediculosis capitis; approved NDA 19-855 for Elimite (1% permethrin) cream for the treatment of scabies.

PHARMACOLOGY AND CONTROLS REVIEWS: These are not as yet available.

Clinical effectiveness studies

I. Study 08-01. This was performed by the following 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 single blind (investigator blind), randomized, parallel group comparison of a single application of Nix cream rinse, eight weekly applications of Nix cream rinse, and eight weekly nonmedicated shampoos in the prophylaxis of head lice infestation in a population heavily infested with head lice (the Cuna Indians of Panama).

2) Patient selection: Those selected were over 2 years of age, and were infested with head lice at the time of entrance into the study.

3) Patient exclusions: Among the exclusions were those with the following conditions:

a. evidence of renal or hepatic impairment.
b. pregnant or nursing women.
c. allergy to the formulation components, pyrethrins, chrysanthemums, or ragweed.
d. current administration of a systemic antimicrobial drug.
e. use of a pediculicide within the week prior to the study or a medicated shampoo within 72 hours prior to the study.
f. an abnormal scalp or hair condition other than pediculosis.

4) Treatment procedures: On entrance into the study the patients were pre-treated with Rid according to the package instructions. At one to five days after pretreatment the patients were examined for live lice, and louse free patients were assigned to one of three treatment arms:

a. single application of Nix cream rinse.
b. eight weekly applications of Nix cream rinse.
c. eight weekly shampoos with Prell shampoo.

Prior to applications of Nix cream rinse the hair was shampooed with Prell. Nix remained on the hair for ten minutes and was then rinsed out with water. (Apparently these procedures were performed by clinical assistants).

5) Effectiveness and safety procedures and parameters: At each weekly return visit during treatment and at two weeks following the end of treatment the patients were examined for the presence of adult head lice and for dermal reactions. If live lice were found, that patient was dismissed from the study as a treatment failure.

The primary measure of efficacy was the time to reinfestation.

Results were as follows.

1) Demographic characteristics: Ninety-two patients were enrolled in the study, of which 88 were evaluable for efficacy. The characteristics of all patients enrolled were as follows.

	(Prell) No permethrin	single permethrin	weekly permethrin
# pts	30	31	31
Age (years)			
	2 (7%)	3 (10%)	3 (10%)
	20 (67%)	19 (61%)	23 (74%)
	8 (27%)	9 (29%)	5 (16%)
Sex			
Female	24 (80%)	18 (58%)	19 (61%)
Male	6 (20%)	13 (42%)	12 (39%)
Race			
Indian	30 (100%)	31 (100%)	31 (100%)

Patients were considered to be evaluable if they returned at minimum for the week 2 visit. By this criterion four patients were not evaluable; these included one each in the weekly permethrin and no permethrin group, and two in the single permethrin group.

2) Efficacy results: The number of patients reinfested during the study period and the median time to reinfestation were as follows (Table 2, pg 244, Vol 2.3).

	(Prell) No permethrin	single permethrin	weekly permethrin
# evaluable pts	29	29	30
# reinfested	27	26	1
Median time to reinfestation (weeks)	1.08	4.75	> 9

In the time to reinfestation following pre-treatment with Rid, single permethrin applications were significantly superior to no permethrin applications ($p \leq 0.05$), and the eight weekly permethrin applications were significantly superior to a single permethrin application and to no permethrin applications ($p \leq 0.05$).

3) Safety results: No adverse experiences and no signs or symptoms of dermal intolerance were recorded.

Reviewer's evaluation: *This study did not use the treatment regimen which is directed in the proposed labeling, namely three applications at two week intervals, but rather used single applications or eight weekly applications of Nix cream rinse. The results are therefore not applicable to the labeling claims for effectiveness.*

II. Study 17-01. This study was performed by the same investigators who conducted study 08-01, as follows.

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 single blind (investigator blind), randomized, parallel group comparison of a single application of Nix cream rinse, Rid, and R&C shampoo in the treatment and prophylaxis of head lice infestation in a population heavily infested with head lice (the Cuna Indians of Panama).

2) Patient selection: Those selected were over 2 years of age, and were infested with head lice at the time of entrance into the study.

3) Patient exclusions: Among the exclusions were those with the following conditions:

a. evidence of renal or hepatic impairment.
b. pregnant or nursing women.
c. allergy to the formulation components, pyrethrins, chrysanthemums, or ragweed.
d. current administration of a systemic antimicrobial drug.
e. use of a pediculicide within the week prior to the study or a medicated shampoo within 72 hours prior to the study.
f. an abnormal scalp or hair condition other than pediculosis.

4) Treatment procedures: Patients assigned to treatment with Nix cream rinse had their hair washed with Prell shampoo, following which Nix was applied and remained on the hair for ten minutes. The patients in the Rid and R&C shampoo treatment groups were treated with these products according to the manufacturer's instructions. The applications were made by clinical assistants.

5) Effectiveness procedures and parameters: Examinations for the presence of live lice or nymphs were made weekly for ten weeks following treatment. Patients with live lice were dismissed from the study as treatment failures.

The primary parameter for prophylactic efficacy was the time to reinfestation.

6) Safety evaluation: At 30-60 minutes after treatment, and at each weekly evaluation for ten weeks, the investigator was to rate the following signs and symptoms as mild, moderate, or severe: edema, erythema, rash, pruritus, burning/stinging, pain, numbness and tingling.

Results were as follows.

1) Demographic characteristics: Ninety-nine patients were enrolled in the study, of which 98 were evaluable for efficacy. The characteristics of all patients enrolled were as follows.

	Nix	Rid	R&C
# pts	33	33	33
Age (years)			
	1 (3%)	2 (6%)	2 (6%)
	26 (79%)	24 (73%)	22 (67%)
	6 (18%)	6 (18%)	8 (24%)
	0	1 (3%)	1 (3%)
Sex			
Male	17 (52%)	14 (42%)	15 (45%)
Female	16 (48%)	19 (58%)	18 (55%)
Race			
Indian	33 (100%)	33 (100%)	33 (100%)

Patients were considered to be evaluable if they returned at minimum for the week 1 evaluation; one patient in the Nix group did not return for this visit.

2) Efficacy results: The number of patients reinfested during the study period, the median time to reinfestation, and the proportion free of lice at two weeks were as follows. (Adapted from Table 2, pg 1942, Vol 7.)

	Nix	Rid	R&C
# evaluable pts	32	33	33
# reinfested	29	33	33
Median time to reinfestation (weeks)	4.4	1.1	0.7
Free of lice at two weeks	94% (30/32)	30% (10/33)	12% (4/33)

In the time to reinfestation, Nix was significantly superior to both Rid and R&C ($p \leq 0.05$).

3) Dermal reactions: All designated signs and symptoms were recorded as absent at all of the evaluations.

Reviewer's evaluation:This study did not use the treatment regimen which is directed in the proposed labeling, namely three applications at two week intervals, but rather used a single application of Nix cream rinse. The results are therefore not applicable to the labeling claims for effectiveness. The study was also performed by the same investigators as the first study.

III. Study 11-01. This was performed by the following investigators.

Ellen Clore, R.N.
Orlando, FL

Doris Wagner, R.N.
Indianapolis, IN

Cecil Smith, D.Ph.
Jackson, TN

Joan DiNapoli, R.N.
Durham, NC

Charles Beal, M.D.
Palo Alto, CA

James Bowerman, M.D.
Phoenix, AZ

Joseph Orthoefer, D.VM
Rockford, IL

The conduct of the study was as follows.

1) Study design: This was a double blind, randomized, parallel group comparison of eight weekly applications of Nix cream rinse and placebo cream rinse in the prevention of head lice infestation. Eighty percent of the subjects were randomized into the Nix group, and 20% were randomized into the placebo group.

2) Patient selection: Those selected were over 2 years of age and were not infested with head lice. Selections at each center were made from the general population of the surrounding community.

3) Patient exclusions: Among the exclusions were those with the following conditions:

a. evidence of renal or hepatic impairment.
b. pregnant or nursing women.
c. allergy to the formulation components, pyrethrins, chrysanthemums, or ragweed.
d. current administration of a systemic antimicrobial drug.
e. use of a pediculicide within the week prior to the study.
f. an abnormal scalp or hair condition other than pediculosis.

4) Treatment procedures: After shampooing with Prell shampoo, Nix cream rinse or the placebo rinse were applied and remained on the hair for ten minutes, then rinsed out with water. This procedure was repeated weekly for eight weeks. Applications were made by the subject or the subject's guardian.

5) Safety and effectiveness procedures: At each weekly return visit the scalp was examined for the presence of live adult lice or nits.

At 30-60 minutes after treatment, and at each weekly evaluation for ten weeks, the investigator rated the following signs and symptoms as mild, moderate, or severe: edema, erythema, rash, pruritus, burning/stinging, pain, numbness and tingling.

Results were as follows.

1) Demographic characteristics: 1701 subjects were enrolled into the study, of which 1659 were evaluated for efficacy. The demographic characteristics of all patients enrolled were as follows.

	Placebo	Permethrin
# pts	340	1361
Age (years)		
	1 (0%)	13 (1%)
	96 (28%)	399 (29%)
	153 (45%)	573 (42%)
	78 (23%)	318 (23%)
	12 (4%)	58 (4%)
Sex		
Male	159 (47%)	664 (49%)
Female	181 (53%)	697 (51%)
Race		
White	215 (63%)	870 (64%)
Black	7 (2%)	20 (1%)
Hispanic	56 (16%)	220 (16%)
Asian	60 (18%)	300 (18%)
Other	2 (0%)	11 (1%)

Forty-two subjects were excluded from all efficacy analyses because of protocol violations, primarily ineligibility at time of entry into the study. An additional 69 subjects were dismissed or dropped out during the course of the study; 7 of these were due to adverse experiences, as described below.

2) Efficacy results: The presence of live lice or nits at a return visit was considered a treatment failure. Seven subjects were regarded by the investigators to be treatment failures; all of these were in the permethrin group. One of these subjects had live lice observed, and six had solely nits. It was felt by the sponsor, on the basis of microscopic examination of the nits in two cases and the absence of symptoms characteristic of infestation in five cases, that the nits in five subjects were from infestation prior to entry into the study. Analysis of the hair from the sixth subject, who had a large number of nits, showed low levels of permethrin, and the sponsor questioned this patient's compliance with the treatment regimen. The one report of live lice was at week 10, two weeks after the last application.

Nits were found in an additional five subjects at one center during the study; these were noted to be more than an inch from the scalp and were considered 'insignificant ' by the investigator.

Statistical analysis did not show a significant difference between the treatment groups (p = 0.19) (presumably in the infestation rate).

3) Safety evaluations: One placebo patient and six permethrin patients discontinued treatment due to adverse experiences, as follows.

	# Subjects	Adverse experience	Severity
Placebo	1	Erythema	Moderate
		Rash	Moderate
		Pruritus	Moderate
Permethrin	2	Pruritus	Mild
		Rash	Mild
	1	Flushing	Mild
		Pruritus	Mild
	1	Rash	Moderate
		Erythema	Moderate
		Pruritus	Moderate
	1	Rash	Mild
	1	Pruritus	Moderate

All of the above adverse experiences with permethrin occurred at a single center (DiNapoli). Patients in the above tabulation of adverse experiences were listed in the tabulation below for dermal effects seen at return visits only if the effects were found at return visits; some of those with adverse experiences discontinued between visits and so are not listed in the tabulation of dermal effects.

The results of the evaluation for designated signs and symptoms showed in the permethrin group 1 or 2 subjects with mild edema, pain, or tingling, and 1 subject with moderate pain. The incidence and maximum recorded severity of the other signs and symptoms were as follows. (Adapted from Table 12, pg 456, Vol 4)

	Mild	Moderate	Severe
Erythema			
Placebo	12 (4%)	2 (1%)	0
Permethrin	42 (3%)	4 (0%)	0

	Mild	Moderate	Severe
Rash			
Placebo	2 (1%)	1 (0%)	0
Permethrin	5 (0%)	3 (0%)	0
Pruritus			
Placebo	6 (2%)	4 (1%)	0
Permethrin	20 (1%)	4 (0%)	2 (0%)
Burning/stinging			
Placebo	3 (1%)	0	0
Permethrin	8 (1%)	0	0
# pts			
Placebo	340		
Permethrin	1361		

Reviewer's evaluation: This study did not use the treatment regimen which is directed in the proposed labeling, namely three applications at two week intervals, but rather used eight weekly applications of Nix cream rinse. The results are therefore not applicable to the labeling claims for effectiveness. The population groups studied at the different centers were also not in a head lice epidemic, as defined in the proposed labeling as an infestation rate of at least 20%, so that the study yielded no conclusive results.

Other information

In vitro studies on the residual pediculicidal effect in hair at intervals after the application of Nix cream rinse have not been reviewed at this time.

Clinical safety studies on systemic tolerance after multiple applications of Nix cream rinse were provided in the original application, and were reviewed in the MOR of October 2, 1985.

Proposed labeling

Summary and evaluation

This supplemental application on Nix cream rinse is felt to be not approvable for the prophylaxis of head lice infestation, on the basis of a lack of demonstration of effectiveness for the proposed labeling claim under the recommended directions for use.

The recommended number of applications is variously stated in the proposed labeling as two or three at two week intervals. It is first stated that prophylactic application should be once every two weeks for a four week period, which would be applications on days 1, 15 and 29. This paragraph continues, however, with directions for two applications for prophylactic use.

Three clinical studies have been provided on prophylaxis of head lice infestation, two of which were performed by the same investigators. The first study was a comparison of single applications of Nix cream rinse, eight weekly applications of Nix cream rinse, and eight weekly applications of a nonmedicated shampoo. The second study was a comparison of a single application of Nix cream rinse with single application of two other pediculicidal products. The third study was a comparison of eight weekly applications of Nix cream rinse with placebo cream rinse. Thus, none of the studies employed the treatment regimen recommended in the proposed labeling, and so they are not applicable to a demonstration of effectiveness in this regard.

Review of the safety for the proposed use is deferred at this time, but it appears that clinical data in the original submission of the application are adequate for the proposed usage.

Recommendations: It is recommended that this supplemental application for Nix cream rinse in the prophylaxis of head lice infestation not be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-340
HFD-520
HFD-520/MO/PHuene/smo/Alpert SA 12/5/91
HFD-520/Pharm/Osterberg
HFD-520/Chem/DeCamp
HFD-520/CSO/RCook MML 4/30/92

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 19-918 Supplement # 004 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: NIX (permethrin) Creme Rinse, 1% Action: (AP) AE NA

Applicant WARNER LAMBERT Therapeutic Class _____

Indication(s) previously approved FOR TREATMENT OF HEAD LICE
Pediatric labeling of approved indication(s) is adequate X inadequate ___

Indication in this application PROPHYLACTIC USE OF NIX DURING HEAD LICE EPIDEMICS
(For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Ray Blay
Signature of Preparer and Title (PM, CSO, MO, other)

10/24/96
Date

cc: Orig (NDA)/PLA # 19918
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

10/31/96

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

NDA 19-918/SE1-004
Warner Lambert Company

Use of Clinical Trials from NDAs 19-918 and 19-435 to support approval of SE1-004.

The following three trials from NDA 19-918 were originally submitted in support of approval of this supplement:

(1) Study # 08-01
(2) Study # 17-01
(3) Study # 11-01

Additionally the following two studies from NDA 19-435 were referenced in support of approval of this supplement:

(4) Study # 01-01
(5) Study # 02-01

All of the above studies (1-5) were originally submitted to IND and were sponsored by The IND is still owned by

In July of 1996, both NDAs were purchased by Warner Lambert.[1]

Because studies (1-3) were not conducted in accordance with labeling directions, the submission (NDA 19-918/SE1-004) was not approved as detailed in the NA letter of June 15, 1992.

In response to the NA letter, the sponsor submitted on December 28, 1992, and March 16, 1993, amendments revising the recommended treatment regimen to that studied in the clinical trials.

The reviewing medical officer then incorporated studies (4) and (5), originally used to support the approval of NDA 19-435, to support the approval of NDA 19-918/SE1-004.

Therefore, the combination of 5 studies (3 in support of the supplement and two more in support of NDA 19-435) are used to support the approval of NDA 19-918/SE1-004.

The above information is also addressed in the supervisory medical officer's review of March 9, 1995, which can be found in Volume 5.1 of the archival jackets for NDA 19-918 and in this action package.

12/24/96

[1]The information outlined in the preceding paragraph was taken from a facsimile sent to me on 10.24.96 by Ms. Tracy Lawhon, Manager, Regulatory Affairs, Warner Lambert Company.

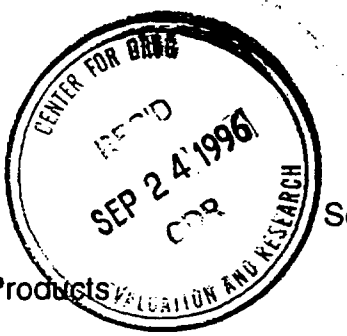
Warner-Lambert Company
170 Tabor Road
Morris Plains, New Jersey 07950

201 540-2000
Cable Address: WARNLAM MORRISPLAINS
Telex: 136424 (WARNERLAM MOPS)

NDA SUPPL AMEND
SE1-004 (AL)

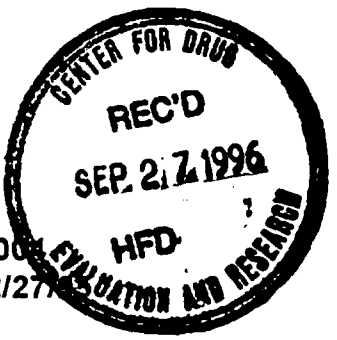
ATTACHMENT 1

WARNER LAMBERT



September 20, 1996

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration, CDER
Central Document Room
Park Building, Rm 214
14240 Parklawn Drive
Rockville, MD 20852



Re: **NDA #19-918 Nix® (permethrin) Creme Rinse, 1% / S-00[illegible]**
Update to Amendment to Supplemental Application, 12/27[illegible]

Dear Dr. Wilkin:

Reference is made to NDA # 19-918 for Nix® (permethrin) Creme Rinse, 1%. Reference is also made to:

• the May 3, 1995 FDA letter issued by the Division of Topical Drug Products pursuant to the review of supplemental application S-004 which provided for the prophylactic use of Nix during head lice epidemics;

• the amendment to the supplemental application submitted December 27, 1995; and

• the telephone conversations between Dr. Roy Blay of the Division and Ms. Eileen Barry of Warner-Lambert Company on July 30, 1996.

During review of the proposed final printed professional labeling and product labeling, FDA recommended that the phrase "for 14 Days" be added to the bulleted point "Prevents Reinfestation" on the principal display panel and side panel of the product labeling.

At this time, we wish to revise our amendment of 12/27/95 by making a commitment to amend the final printed labeling to incorporate the phrase "for 14 Days" as recommended. The amended product labeling, which includes this revision is provided in Attachment 1 (carton labels) and Attachment 2 (bottle label). In addition, since the product is now owned and distributed by Warner-Lambert, the distributor statement and "heritage statement" (on the bottom panel of the carton) have been revised accordingly.