CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75014

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-014

Date of Submission: October 7, 1999 and October 15, 1999 (Amendments)

Applicant's Name: Alpharma, U.S. Pharmaceuticals Division

Established Name: Permethrin Lotion, 1%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 2 fl oz (59 mL)

Satisfactory as of October 7, 1999 submission

Carton Labeling: (1 x 59 mL and 2 x 59 mL)

Satisfactory as of October 7, 1999 submission

Professional Labeling: Satisfactory as of October 15, 1999 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Nix Crème Rinse, 1%

NDA Number: 19-918

NDA Drug Name: Permethrin Lotion, 1%

NDA Firm: Warner-Lambert Company

Date of Approval of NDA Insert and supplement #004: November 1, 1996

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison

Basis of Approval for the Carton Labeling: Side-by-side comparison

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	

Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based on the labeling for the reference listed drug (Nix Crème Rinse, 1% - Warner Lambert Company; approved November 1, 1996; acknowledged and retained September 23,1999).

2. This is the first generic for this drug product.

3. Labeling
   Although the applicant refers to its product as a "crème rinse" as does the RLD, Alpharma has been asked to revise this to read "lotion" to be in accord with the name used in the Orange Book.

   OGD received a telephone call from Mike Benson in Div of OTC Drug Products. He wanted to alert us of extensive changes expected to occur in the labeling for pediculocides within the next two months.

   There is also professional labeling that accompanies this product which was not included in the original labeling sent to us by HFD-560. On August 25, 1999, Don Hare and Lillie Golson met with HFD-560 and HFD-540 concerning this labeling. We learned that even though the product will have the same carton labeling – this prophylactic indication is not on the carton– this professional insert is to be made available to practitioners, but is not to accompany the product for consumer's to use. Since this labeling piece is only used with the prophylactic use in head lice epidemics indication, Alpharma has been asked to make this labeling available after the exclusivity expiration date of November 1, 1999. In the meantime, Babette Merrit, the PM of OTCs, is to check with Warner Lambert to see if the labeling is still being used.

Ron Bynum of Alpharma telephoned and wanted guidance on the distribution of the professional labeling piece. He suggested putting on the Internet, including a statement on the insert. I indicated that I would try to get an answer for him.

I telephoned Marina Chang and mentioned the two proposals made by Alpharma. He indicated that neither would be acceptable, but still did not offer any suggestions. On October 1, 1999, I e-mailed Babette Merritt, the PM for this product and requested that someone over there simply telephone Warner Lambert. I am still waiting for a response. In the meantime, Alpharma indicated in its amendment letter that the insert would be forwarded to practitioners using methodologies available to the firm (whatever that means).

Mike Benson left a message concerning the distribution of the "professional labeling" for the Nix Crème Rinse. He and Babette Merritt had a conference call with Warner-Lambert Friday, 10/8/99. Warner-Lambert indicated that they distribute this information in the following ways: Direct mailings to MDs, RNs and RPhs; detail MDs at a "Lunch and Learn" program; advertise in professional journals; put info in OTC PDR. When John Grace was made aware of this, he questioned even more whether or not this information is truly "labeling" according to the ACT. He indicated that legal counsel should be sought on this.

Peter Rickman was consulted on this 10/14/99. Among Peter, John and me, we decided to contact Martin Levy of Alpharma, apprise him of the mechanisms Warner-Lambert uses to get information out on the prophylaxis indication, allow them to place it on Alpharm's web site, and have Alpharma submit the labeling piece ASAP for review. Since it is unlikely that the application would be approved before November 1, Mr. Levy will be asked to submit the piece ASAP so that everything can be reviewed and approved together.

4. USP Issues
Not a USP item
RLD – Store at 15-25°C (59-77°F).
ANDA – Same as RLD

5. Bioequivalence Issues – Product deemed bioequivalent September 14, 1999.

6. Patent/Exclusivity Issues
This product has market exclusivity for prophylactic use during head lice epidemics until November 1, 1999.

Date of Review:
October 19, 1999

Date of Submission:
October 7, 1999 and October 15, 1999 (Amendments)

Primary Reviewer:

/S/

Date:

Secondary Reviewer:

Date:

Team Leader:

/S/

Date:

10/19/1999

cc: ANDA: 75-014
DUP/DIVISION FILE
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Review

Concur
/S/ 10/20/99

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-014 Date of Submission: September 29, 1999 (Amendment)

Applicant's Name: Alpharma, U.S. Pharmaceuticals Division

Established Name: Permethrin Lotion, 1%

Labeling Deficiencies:

CARTON (1 x 59 mL and 2 x 59 mL)

Satisfactory in draft

Please submit your labels and labeling in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following web site for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see			

ASHP guidelines)			
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	

Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. Labeling review based on the labeling for the reference listed drug (Nix Crème Rinse, 1% - Warner Lambert Company; approved November 1, 1996; acknowledged and retained September 23,1999).

2. This is the first generic for this drug product.

3. Labeling
Although the applicant refers to its product as a "crème rinse" as does the RLD, Alpharma has been asked to revise this to read "lotion" to be in accord with the name used in the Orange Book.

OGD received a telephone call from Mike Benson in Div of OTC Drug Products. He wanted to alert us of extensive changes expected to occur in the labeling for pediculocides within the next two months.

There is also professional labeling that accompanies this product which was not included in the original labeling sent to us by HFD-560. On August 25, 1999, Don Hare and Lillie Golson met with HFD-560 and HFD-540 concerning this labeling. We learned that even though the product will have the same carton labeling – this prophylactic indication is not on the carton– this professional insert is to be made available to practitioners, but is not to accompany the product for consumer's to use. Since this labeling piece is only used with the prophylactic use in head lice epidemics indication, Alpharma has been asked to make this labeling available after the exclusivity expiration date of November 1, 1999. In the meantime, Babette Merrit, the PM of OTCs, is to check with Warner Lambert to see if the labeling is still being used.

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4. **USP Issues**
Not a USP item
RLD – Store at 15-25°C (59-77°F).
ANDA – Same as RLD

5. **Bioequivalence Issues – Product deemed bioequivalent September 14, 1999.**

6. **Patent/Exclusivity Issues**
This product has market exclusivity for prophylactic use during head lice epidemics until November 1, 1999.

Date of Review:
October 5, 1999

Date of Submission:
September 29, 1999 (Amendment)

Primary Reviewer:

Date:

Team Leader: /S/

Date: 10/6/1999

/S/

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cc:

ANDA: 75-014
DUP/DIVISION FILE
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-014 Date of Submission: July 16, 1999 (Amendment)

Applicant's Name: Alpharma, U.S. Pharmaceuticals Division

Established Name: Permethrin Lotion, 1%

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We note that your Patent Certification and Exclusivity Statement is not accurate. Please submit an updated Patent Certification and Exclusivity Statement. We refer you to the 19th edition of the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book).

   b. Be reminded that the labeling format will soon change to comply with the new OTC Format regulations. Please monitor the OGD web site mentioned below for changes.

(410) 538-7253

2. CONTAINER - 2 fl oz (59 mL)

   Satisfactory in draft

3. CARTON (1 x 59 mL and 2 x 59 mL)

   Delete "FULL PRESCRIPTION STRENGTH" appearing on the principal display and end panels.

4. INSERT

   Please note that Nix has marketing exclusivity for "prophylactic use during head lice epidemics" until November 1, 1999. After that time, the attached professional labeling is to be made available to health care practitioners using Nix for this indication.

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following web site for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Nix Professional Insert Labeling

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
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Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
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Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents		X	

appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. Labeling review based on the labeling for the reference listed drug (Nix Crème Rinse, 1% - Warner Lambert Company; approved November 1, 1996).

2. This is the first generic for this drug product.

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4. USP Issues
Not a USP item
RLD – Store at 15-25°C (59-77°F).
ANDA – Same as RLD

5. Bioequivalence Issues – pending

6. Patent/Exclusivity Issues
This product has market exclusivity for prophylactic use during head lice epidemics until November 1, 1999.

Date of Review:
September 21, 1999

Date of Submission:
July 16, 1999 (Amendment)

Primary Reviewer:

Date:

Team Leader:

/S/

Date: 9/24/1999

cc:

ANDA: 75-014
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-014 Date of Submission: December 30, 1998

Applicant's Name: Alpharma, U.S. Pharmaceuticals Division

Established Name: Permethrin Lotion, 1%

Labeling Deficiencies:

1. CONTAINER - 2 fl oz (59 mL)

   a. The established name of this product is "permethrin lotion". Revise your labeling to be in accordance. Also include the product's concentration, "1%".

   b. Ensure that the established name and concentration appear as the most prominent information on the label.

2. CARTON (1 x 59 mL and 2 x 59 mL)

   See CONTAINER comments.

Please revise your labels and labeling, as instructed above, and submit in draft.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. Labeling review based on the labeling for the reference listed drug (Nix Crème Rinse, 1% - Warner Lambert Company; approved November 1, 1996).

2. This is the first generic for this drug product.

3. Labeling

Although the applicant refers to its product as a "crème rinse" as does the RLD, Alpharma has been asked to revise this to read "lotion" to be in accord with the name used in the Orange Book.

The labeling for the applicant differs from that approved November 1, 1996, for the RLD. However, OGD received a telephone call from Mike Benson in Div of OTC Drug Products.

He wanted to alert us of extensive changes expected to occur in the labeling for pediculocides within the next two months. Bearing this in mind, Alpharma was not asked to revise their labeling at this time pending approval of the proposed labeling changes for the RLD.

Alpharma was also reminded that the final rule for OTC labeling was in effect and that the next submission should be revised accordingly.

4. USP Issues

Not a USP item

RLD - Store at 15-25°C (59-77°F).

ANDA - Same as RLD

5. Bioequivalence Issues - pending

6. Patent/Exclusivity Issues

Exclusivity protection for prophylactic use during head lice epidemics until November 1, 1999. In the labeling itself, it is difficult to discern what part applies to the prophylactic use of this product. The only thing that was omitted from the applicant's labeling was the bullet "prevents re-infestation for 14 days" which really does not seem to apply to this issue either.

Date of Review:
June 6, 1999

Date of Submission:
December 30, 1998

Primary Reviewer:
/S/

Date:
6/10/99

Team Leader:
/S/

Date:
~~6/10/1999~~
6/11/1999

HFD-540 Trac No:993354
Consult # 88

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 24, 1999

FROM: Phyllis A. Huene, M.D.
Medical Officer
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Susan Walker, M.D. /S/ 7/22/99
Team leader, Dermatology
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Jonathan Wilkin, M.D. /S/ 7/30/99
Director
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Robert DeLap, M.D. /S/ 8/19/99
Director
Office of Drug Evaluation II (HFD-105)

TO: Linda Katz, M.D.
Division of OTC Drugs
(HFD-560)

SUBJECT: ANDA 75-014
1% permethrin lotion (creme rinse)

Date of request: 5/20/99

Dr. Mary Fanning of the Office of Generic Drugs has completed a review of a clinical study to compare the safety and effectiveness of 1% permethrin lotion (Alpharma Pharmaceuticals) to Nix creme rinse in the treatment of pediculosis capitis. Dr. Fanning recommended that this study be sent to DDDDP for review, and for comments on the primary efficacy endpoint.

The study was a double blind, randomized, parallel group comparison of the two test products in 111 patients in the Republic of Panama. For entry into the study the patients were to have at least 6 adult lice or nymphs, and at least 20 eggs which were viable in appearance. The test products were applied to the scalp and hair by trained staff, and left in place for ten minutes, then rinsed out. The rinse water was processed for louse counts, and 10 hairs with attached eggs were collected. At 7 and 14 days after treatment the patients were examined for the presence of live adult lice or nymphs, and for viable eggs. Safety was assessed by examination of the skin and scalp at 30 to 60 minutes after treatment for erythema or other effects, and evaluation of symptoms such as burning, numbness, or stinging.

In the protocol a Treatment Success was considered to be the primary endpoint; this was defined as no lice or viable eggs at days 7 and 14.

The patients were otherwise classified as a Treatment Failure, defined as live lice at any stage on day 7 or more than 5 adult lice or any nymphs at day 14, or as Reinfestation, defined as no lice or viable eggs at day 7, but adult lice at day 14. The sponsor later introduced in the study report the classification of Treatment Cure, defined as both Treatment Success and Re-infestation.

The only population that was analyzed in the study report was the ITT population. Dr. Fanning notes that an efficacy valid, rather than an ITT population, is used for the analysis of a bioequivalence study.

The sponsor found that for the ITT population the two treatments were not therapeutically equivalent in the percentage of patients with Treatment Success, because the Alpharma product was superior to Nix. Apparently this result prompted the sponsor to introduce Treatment Cure as the primary endpoint, defined as including both Treatment Success and Reinfestation. Since Nix had 3 cases of re-infestation that were now included among those meeting the endpoint and the Alpharma product had no cases of re-infestation, this made the Nix product appear more efficacious, and bioequivalence was achieved.

Dr Fanning extracted the data for the efficacy valid population and subjected these to an equivalence analysis. She found that a Treatment Success was found in 44/51 (86%) treated with the Alpharma product and in 38/51 (75%) treated with Nix. Her conclusion was that the Alpharma product was more efficacious than Nix, and so the two are not bioequivalent. When the proportion of

patients with a Treatment Cure (as defined above) were compared, the two products were bioequivalent.

None of the patients experienced local signs or symptoms, and other adverse events were unrelated to the study products.

Reviewer's evaluation: It is felt that the primary efficacy endpoint should be Treatment Success for the Per Protocol population, where Treatment Success is defined as the absence of live lice or eggs at days 7 and 14. Bioequivalence is demonstrated when the innovator product is shown to be not inferior to the reference drug product. This means that the innovator product may be superior to the reference product.

By these criteria it is felt that bioequivalence has been demonstrated between the Alpharma product and Nix creme rinse.

It is noted that bioequivalence studies on dermatologics should have a placebo (vehicle) group in order to eliminate observer bias. However, a bioequivalence study on permethrin cream for scabies which did not include a placebo group was previously accepted by the Office of Generic Drugs, as have been other such bioequivalence studies.

/S/ , M.D.

Phyllis A. Huene, M.D.

6/28/99

cc: HFD-540 Division Files
HFD-540/Wilkin
HFD-540/Walker Sw 7/22/99
HFD-540/Huene
HFD-540/Kozmafornaro

While I do not accept that noninferiority demonstrates bioequivalence, I concur that bioequivalence has been demonstrated for the efficacy signal for these two products and both products allowed 4 and 48 AEs. AW

Return to

MEETING MINUTES

Meeting Date: March 26, 1997 **Time:** 10:00 a.m.

Location: MPN II - Conference Room "B"

Drug Name/ANDA No.: Permethrin Lotion 1%/ANDA 75-014

External Participants: ALPharma USPD, Inc.

Meeting Chair: Gordon Johnston

External Participant Lead: Stanley Kaplan, Ph.D.

Meeting Recorder: Lizzie Sanchez, Pharm.D., Project Manager

FDA Attendees, titles and offices:

Gordon Johnston	Deputy Director, OGD
Jerry Phillips	Director, DLPS
Nicholas Fleischer, Ph.D.	Director, DBE
Mary Fanning, M.D.	Ass. Director Medical Affairs
Peter Rickman	Regulatory Support Branch
Surendra Shrivatava, Ph.D.	Reviewer, DBE
Paul Schwartz, Ph.D.	Chemist, Branch III
Robert West	Deputy Director, DLPS
Cecilia Parise	Project Manager, Regulatory Support
Saundra Middleton	CST, Regulatory Support

ALPharma Attendees, titles and offices:

Stanley A. Kaplan, Ph.D.	Sr. Vice President, R & D
William Clements	Vice President, Regulatory & QA
Michael Baaske, Ph.D.	Sr. Director, Analytical R & D
Subhas Kundu, Ph.D.	Sr. Director, Product Development
Robert Shumaker, Ph.D.	Director, Clinical Studies
Robert Pollock	Lachman Consulting Services

Meeting Objectives:

The meeting was held to give ALPharma the opportunity to discuss the issues raised in the refuse to file letter dated February 13, 1997 received for this application. The formulation used for bioequivalence studies was not the same as the formulation they intend to submit in an application.

Discussion Points:

1. The firms stated their intent to cover the following topics during this discussion:

   a. support the quantitative composition of protein hydrolysate and hydroxyethyl cellulose in the formulation (in amounts exceeding those listed in the Inactive Ingredients Guide, IIG),

   b. discuss the role of propylene glycol (PG) in the formulation (which exceeds the amount found in the RLD),

   c. justify the ex-vivo study which will support this application (to demonstrate clinical equivalence between their initial and revised formulations).

2. ALPharma stated that the changes in formulation occurred as an attempt to improve the pharmaceutical elegance of the product. They stated that their initial analysis of the reference product was not very specific and unable to quantitate certain of the inactive ingredients. The firm reanalyzed the RLD, to better quantitate inactive ingredients.

3. The firm showed several products (generally OTC products) with the same concentration of hydroxyethyl cellulose. It acts as a conditioner.

4. The animal protein was also added as a conditioner. Nix^{R} (the RLD), contains % of hydrolyzed protein (the test product contains %). The firm showed several OTC shampoo products with as much as %.

5. The firm stated that PG generally improves drug penetration. Various products contain from % of PG. The test product contains %. Data were presented to show that the % concentration in the proposed formulation would have little effect on absorption. PG was used as a solvent for the parabens.

6. The product was reformulated because after 6 months of stability testing with the original formulation, the firm noted that the emulsion was creaming. There was also partitioning of the drug into the plastic container, with an apparent decrease of drug concentration over time. To overcome this, the firm increased the cetyl alcohol to %, which is the same amount the innovator product contains. The firm also tried packaging the product in a fluorinated bottle (which is less permeable), but there was still partitioning of the drug into the bottle, although to a lesser extent. After 1 year of stability testing with the

new formulation, there have been no problems of creaming of the product and partitioning into the plastic bottle.

7. The firm conducted toxicological testing and no adverse effects were reported with the above mentioned changes in the formulation. The firm stated they also consulted the CDER Inactive Ingredients Guide.

8. The firm performed in vivo and in vitro studies with their product. The studies were performed in Panama, where lice are endemic. The subjects were treated with the lotion for 10 minutes and the lotion was rinsed. Hair was collected from the subjects prior and after treatment with the lotion (treated and non-treated) into vials. The collected hairs were incubated for 14 days at room temperature and evaluated for ovicidal activity. Subjects were also evaluated after 14 days.

9. After the formulation change, an ex-vivo study was performed from the same population of subjects and investigators. Hair samples were collected, (treated or not) and activity was evaluated. They also looked at killing of lice by submerging live lice in test and reference products, i.e., vehicle without permethrin and water. Egg viability was also examined by microscope. The firm feels that the ex-vivo study could be equivalent to the in-vivo study and would serve as a bridge to the in-vivo study. This ex-vivo study methodology has not been validated by others.

10. The firm presented the outcome data on ovicidal %) and pediculicidal (%) activity (see handout). The firm feels that the clinical outcomes do not change with the change in the formulation. ALPharma wants the application filed, so that this methodology can be evaluated, since they strongly feel that this alternative methodology merits consideration.

11. **FDA Comments**: The "ex-vivo" study needs some changes in design. Consideration should have been given to: an exposure method which mimics the in-vivo situation; evaluation of the effect of permethrin on nymphs and adults separately using a standardized louse colony or colonies; comparison of dose-response curves (ldp lines - log-dose probit mortality curves, a standard method used to compare the toxicity of pesticides in insects) for test and reference products; evaluation of mortality of nymphs and adults for longer duration than one hour (preferably 4 hours); including the effect of pre-treatment hair wash (dilution) on the effectiveness of the products; and evaluating differences in residual ovicidal or pediculicidal activity of the formulations (some formulations may leave residual permethrin in the hair/skin more than others- permethrin is quite lipophilic and stable).

The use of patients and in-vitro samples may be considered as validation for the ex-vivo method.

The firm was advised to include any published articles of the investigators who conducted this study describing the methodology, design and validation when filing.

Decisions (agreements) reached:

The firm will respond to the refuse-to-file letter. A decision to accept the application will be deferred until such a decision is reached. Explanations and safety data to justify those ingredients in excess of the IIG amounts need to be provided. The data will likely be consulted to a toxicologist in NDE if a decision is made to file the application. The more significant issue of the firm's intent to market a formulation that was not the subject of a bioequivalence study needs further discussion within the OGD and OPS. In particular, further evaluation of the ex-vivo study will be performed to determine its relevance.

Unresolved issues or issues requiring further discussion:

Acceptability of application for filing.

Signature, Minutes Preparer: /S/ D. 4/15/97

Concurrence Chair: /S/ by 4-17-97
Date

Draft

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 10, 1997

FROM: Cecelia Parise
Consumer Safety Office
Office of Generic Drugs

SUBJECT: ANDA 75-014
Alpharma
Permethrin Lotion 1%

TO: The Record

Alpharma submitted an application for Permethrin Lotion 1% (Creme Rinse). Alpharma performed an *in vivo* bioequivalence study with one formulation, for which they are not seeking approval. They reformulated the product and have requested a waiver of *in vivo* bioequivalence for the reformulated product and have supported this with *ex vivo* data.

Surrendra Shrivastava and Rabi Patnaik reviewed the change in formulation. The firm increased the amount of cetyl alcohol in their formulation from % w/w, to % w/w. Surrendra and Rabi agreed that the firm would need to provide a new in vivo bioequivalence study to support the change in formulation.

In addition, two of the active ingredients in Alpharma's formulation (protein hydrolysate and hydroxy ethyl cellulose) are in a concentration higher than has been previously approved in a topical drug product.

The Division of Bioequivalence also expressed concern regarding the concentration of propylene glycol in the proposed product. The proposed product contains % w/w propylene glycol and the reference listed drug contains % propylene glycol. However, this is not a refuse to file issue since the concentration of propylene glycol for the proposed product is within the concentration range listed in the IIG for topical products.

ANDA 75-014
Permethrin Lotion 1%
Alpharma

The firm will be notified in a refuse to file letter regarding the inactive ingredients that exceed the previously approved concentration for topical drug products. In addition, they will be informed that the propylene glycol concentration should be the same as the reference listed drug, since propylene glycol is known to be an absorption enhancer, and may increase the absorption of the active ingredient. The firm will also be informed that they must reformulate their product and must provide a new *in vivo* bioequivalence study with their reformulation.

Concur:

Peter Rickman /S/ 2/11/97

Surrendra Shrivastava /S/ 2/12/97

Rabi Patnaik /S/ 2/12/97

Patent and Exclusivity Search Results from query on 019918 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019918	**001**	**I-170**	**NOV 01,1999**

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

TELEPHONE MEMO

To: Ronald Bynum (Alpharma USPD)
(410) 558-7250 Ext. 208

Subject: ANDA 75-014 Permethrin Lotion

From: Joseph Buccine & Paul Schwartz

Date: November 30, 1999

Following tertiary cmc review, Mr. Bynum was asked to make the following changes:

1. FDA is not accepting packaging interchangeability protocols at this time. Please delete reference to this protocol in the ANDA.

2. Please describe the container fluorination procedure, the resin, and level 5 fluorination. Is there residual fluorine in the product? Has the container ever been used in an approved drug product.

Please provide your response in the form of a t-amendment.

Cc:

ANDA
T-con Binder

FROM THE DESK OF...
SAUNDRA T. MIDDLETON
CONSUMER SAFETY OFFICER
CDER\FDA\OGD\DLPS
7500 STANDISH PLACE
ROCKVILLE MD 20855

301-827-5862
Fax: 301-594-1174

ALPHARMA
U.S. Pharmaceuticals Division

Permethrin Lotion, 1%
ANDA #75-014

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA's Atlanta District Office.

Ronald Bynum
Ronald Bynum
Manager, Regulatory Affairs

6/4/97
Date

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
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Baltimore, MD 21224
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Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

Permethrin Lotion, 1%
ANDA #75-014

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96 (b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA's Atlanta District Office.

Ronald Bynum
Ronald Bynum
Manager, Regulatory Affairs

12/30/98
Date

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