

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074806

Trade Name : PERMETHRIN CREAM 5%

Generic Name: Permethrin Cream 5%

Sponsor : Alpharma, U.S. Pharmaceuticals Division

Approval Date: January 23, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074806

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074806

APPROVAL LETTER

JAN 23 1998

Alpharma, U.S. Pharmaceuticals Division
Attention: Ronald Bynum
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated December 12, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Permethrin Cream, 5%.

Reference is also made to your amendments dated June 5, 1996, August 11, 1997, and January 7, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Permethrin Cream, 5% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Elimite Cream, 5% of Glaxo Wellcome Incorporated).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 2

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,



/S/

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

1/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074806

FINAL PRINTED LABELING

PERMETHRIN
CREAM 5% w/w

ALPHARMA
NDC 0472-0242-60



PERMETHRIN CREAM 5% w/w

60 g (2.2 oz)

CAUTION: Federal law prohibits dispensing without prescription.
FOR EXTERNAL USE ONLY •
NOT FOR USE IN EYES

ACTIVE INGREDIENT: Each gram contains permethrin 50 mg (5%).
INACTIVE INGREDIENTS: Butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.
DOSAGE: Thoroughly massage cream into the skin from the head to the soles of the feet. **ONE APPLICATION IS GENERALLY CURATIVE.** Refer to accompanying literature for complete prescribing information.
Keep this and all drugs out of the reach of children.

Store at controlled room temperature 15°-30°C (59°-86°F).
See carton or crimp of tube for lot number and expiration date.
02420990A1 1448600 5259 BC 1 VC-00832

Manufactured by **Alpharma USPD Inc.**, Baltimore, MD 21244
NDC 0472-0242-60





NDC 0472-0242-60

PERMETHRIN CREAM 5% W/W

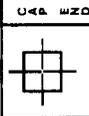
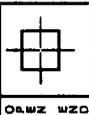
60 g (2.2 oz)

CAUTION: Federal law prohibits dispensing without prescription.
FOR EXTERNAL USE ONLY •
NOT FOR USE IN EYES



SLEEVE LENGTH 5 3/8"

MAX. PRINT AREA 4 9/16"



NDC 0472-0242-60

PERMETHRIN CREAM 5% W/W

FRONT PANEL

MAX PRINT AREA
3.421"

CAUTION: Federal law prohibits dispensing without prescription

FOR EXTERNAL USE ONLY •
NOT FOR USE IN EYES

60 g (2.2 oz)

ACTIVE INGREDIENT: Each gram contains permethrin 50 mg (5%)

INACTIVE INGREDIENTS: Butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isotropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.

DOSEAGE: Thoroughly massage cream into the skin from the head to the soles of the feet. ONE APPLICATION IS GENERALLY CURATIVE. Refer to accompanying literature for complete prescribing information.
Keep this and all drugs out of the reach of children.

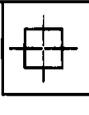
Store at controlled room temperature 15°-30°C (59°-86°F).

See crimp of tube for lot number and expiration date.

022096A1 14761600-5259 BC-1 VC1158

Manufactured by Alpha Pharma USP Inc., Baltimore, MD 21244

BACK PANEL



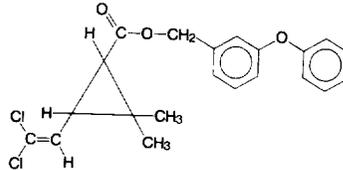
ALPHARMA USP GRAPHICS DIE P5324 0996 AV 410 288-1000 X671	PROOFREAD BY:	PROOFREAD BY:	PANTONE BLACK
8L 1 3/4" x 5 1/4" • 3/4" x 5/16" EE 0242096A1 0242 60.DXD VC1158 09/23/86 DL	DATE:	DATE:	PANTONE 116
	PROOFREAD BY:	PROOFREAD BY:	PANTONE 2593
	DATE:	DATE:	PANTONE 541
	APPROVED	REJECTED	
FDA SAMPLE			



PERMETHRIN CREAM 5%

DESCRIPTION

Permethrin Cream 5% is a topical scabidical agent for the treatment of infestation with *Sarcoptes scabiei* (scabies). It is available in an off-white, vanishing cream base. Permethrin cream is for topical use only.



Chemical Name: The permethrin used is an approximate 1:3 mixture of the cis and trans isomers of the pyrethroid (\pm)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Permethrin has a molecular formula of $C_{21}H_{20}Cl_2O_3$ and a molecular weight of 391.29. It is a yellow to light orange-brown, low melting solid or viscous liquid.

Each gram contains permethrin 50 mg (5%) and the inactive ingredients butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.

CLINICAL PHARMACOLOGY

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

Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine. Although the amount of permethrin absorbed after a single application of the 5% cream has not been deter-

mined precisely, data from studies with ^{14}C -labeled permethrin and absorption studies of the cream applied to patients with moderate to severe scabies indicate it is 2% or less of the amount applied.

INDICATIONS AND USAGE

Permethrin cream is indicated for the treatment of infestation with *Sarcoptes scabiei* (scabies).

CONTRAINDICATIONS

Permethrin cream is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin.

WARNINGS

If hypersensitivity to permethrin cream occurs, discontinue use.

PRECAUTIONS

General: Scabies infestation is often accompanied by pruritis, edema and erythema. Treatment with permethrin cream may temporarily exacerbate these conditions.

Information for Patients: Patients with scabies should be advised that itching, mild burning and/or stinging may occur after application of permethrin cream. In clinical trials, approximately 75% of patients treated with permethrin cream who continued to manifest pruritis at 2 weeks had cessation by 4 weeks. If irritation persists, they should consult their physician. Permethrin cream may be very mildly irritating to the eyes. Patients should be advised to avoid contact with eyes during application and to flush with water immediately if permethrin cream gets in the eyes.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice

when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies.

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

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

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

Pediatric Use: Permethrin cream is safe and effective in pediatric patients two months of age and older. Safety and effectiveness in pediatric patients less than two months of age have not been established.

ADVERSE REACTIONS

In clinical trials, generally mild and transient burning and stinging followed application with permethrin cream in 10% of patients and was associated with the severity of infestation. Pruritis was reported in 7% of patients at various times post-application. Erythema, numbness, tingling, and rash were reported in 1 to 2% or less of patients (see PRECAUTIONS: General).

OVERDOSAGE

No instance of accidental ingestion of permethrin cream has been reported. If ingested, gas-

tric lavage and general supportive measures should be employed.

DOSAGE AND ADMINISTRATION

Adults and children: Thoroughly massage permethrin cream into the skin from the head to the soles of the feet. Scabies rarely infests the scalp of adults, although the hairline, neck, temple, and forehead may be infested in infants and geriatric patients. Usually 30 grams is sufficient for an average adult. The cream should be removed by washing (shower or bath) after 8 to 14 hours. Infants should be treated on the scalp, temple and forehead. ONE APPLICATION IS GENERALLY CURATIVE.

Patients may experience persistent pruritus after treatment. This is rarely a sign of treatment failure and is not an indication for retreatment. Demonstrable living mites after 14 days indicate that retreatment is necessary.

HOW SUPPLIED

Permethrin Cream 5% (wt./wt.) is supplied in 60 g tubes.

Store at controlled room temperature 15°-30° C (59°-86° F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Alpharma USPD Inc.
Baltimore, MD 21244

FORM NO. 0242
Rev.9/96 B1

VC1257

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074806

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.2
2. ANDA # 74-806
3. NAME AND ADDRESS OF APPLICANT

Alpharma, U.S. Pharmaceuticals Division
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that patent 4024163 held by Burroughs Wellcome Co. will expire on May 17, 1996.

The firm indicates that there is no reference to marketing exclusivity for the referenced product and they will not introduce the product into the marketplace prior to expiration of the patent on May 17, 1996.

- | | |
|-------------------------------|---|
| 5. <u>SUPPLEMENT(s)</u> | 6. <u>PROPRIETARY NAME</u> |
| N/A | N/A |
| 7. <u>NONPROPRIETARY NAME</u> | 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> |
| Permethrin | N/A |

9. AMENDMENTS AND OTHER DATES:

Original 12/12/95
Amendment 2/19/96
Amendment 3/5/96
Amendment 10/10/96
Amendment 1/7/98

- | | |
|---------------------------------------|----------------------|
| 10. <u>PHARMACOLOGICAL CATEGORY</u> | 11. <u>Rx or OTC</u> |
| Treatment of infestation with scabies | Rx |

12. RELATED IND/NDA/DMF(s)

DMF 's [REDACTED] (b)4 - [REDACTED]

- | | |
|------------------------|--------------------|
| 13. <u>DOSAGE FORM</u> | 14. <u>POTENCY</u> |
|------------------------|--------------------|

Cream 5%

15. CHEMICAL NAME AND STRUCTURE

(3-phenoxyphenyl)methyl(1RS)-cis,trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D.

11/6/97

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 74-806
Division File
Field Copy

Endorsements:

HFD-627/NNashed/11/6/97 1/8/98
HFD-627/PSchwartz/11/6/97 P.S. 1/8/98
X:\NEWFIRMSAMALPHARMALTRS&REV\74-806.2
F/t by: gp/11/14/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074806

BIOEQUIVALENCE REVIEW(S)

OCT 23 1997

Permethrin Cream 5%
Topical
ANDA #74-806
Reviewer: Moheb H. Makary
WP 74806S.997

Barre-National Incorporated
Baltimore, MD
Submission Date:
September 2, 1997

Addendum To The June 4, 1997 Review

This application was originally was found to be acceptable pending an acceptable inspection report supporting that the conduct of the study conformed to good clinical practices (submission dated June 4, 1997). However, the Division of Scientific Investigations (DSI) could not investigate and verify the data submitted to the FDA, and recommended that the data should not be used as the sole basis for approval of any efficacy and safety claims made by the sponsor in the ANDA. Therefore, the study for lack of verification was determined to be unacceptable to the Division of Bioequivalence.

On September 2, 1997, the Division of Scientific Investigations (DSI), sent an inspection report to the Division of Bioequivalence regarding ANDA #74-806. In summary, this study was found to be well conducted and the validated data were acceptable to support ANDA #74-806. Therefore, the recommendation made by the Division of bioequivqalence dated June 6, 1997 should be changed to acceptable.

Inspector's Findings

1. There were no significant discrepancies between the Case Report Form (CRF) data and the data listing submitted to the ANDA, both for documentation to assure that all audited subjects did exist and were alive for the duration of the study.
2. Each of the 132 CRF contained signed informed consent forms.
3. The protocol used in the conduct of the study was identical to the protocol submitted in the ANDA.

Recommendation:

The study inspection did ascertain that the study was conducted in accordance with good clinical practices and did verify the data submitted in the ANDA. Therefore, the firm's clinical study conducted on its Permethrin Cream 5% has been found acceptable by the Division of Bioequivalence. The study demonstrates that Barre's Permethrin Cream 5%, is bioequivalent to Glaxo Wellcome's Elimate® Cream, 5%.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 10/10/97

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/

Date: 10/10/97

/S/

Concur: _____
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 10/23/97

Mmakary/9-8-97, 10-10-97 wp 74806S.997
cc: ANDA #74-806, original, HFD-650 (Director), HFD-658 (Makary),
Drug File, Division File.

3-1
JUN -6 1997

Permethrin Cream 5%
Topical
ANDA #74-806
Reviewer: Moheb H. Makary
WP 74806S.697

Barre-National Incorporated
Baltimore, MD
Submission Date:
June 4, 1997

Amendment to the Consultative Review of Clinical Bioequivalence
Study of February 16 and June 15, 1996

The approval of this application was pending an acceptable inspection report supporting that the conduct of the study conformed to good clinical practices. The Division of Bioequivalence requested the Division of Scientific Investigations (DSI) to conduct an inspection of the study site in Panama. On April 9, 1997, Dr. Lepay (DSI-Division Director) authorized an audit inspection for the study's data that were collected in Panama.

Inspector's Findings

1. The inspector had no access to medical records. Health status was determined by extensive questioning of the patients.
2. Data verification upon Case Report Forms could not be obtained at the study site. The firm claimed that upon completion of the study all information was directly entered on the case report forms and shipped to the (b)4 - Confidential Business. A visit to Panama for the purposes of a data audit was not warranted.

Inspector's Recommendation

The Division of Scientific Investigations (DSI) could not verify the data submitted to the FDA. Therefore, the data cannot be used as the sole basis for approval of any efficacy and safety claims made by the sponsor in the ANDA.

Reviewer's Comment

The reviewer agrees with inspector's recommendation.

Recommendation:

The study inspection did not ascertain that the study was conducted in accordance with good clinical practices and did not verify the data submitted in the ANDA. Therefore, the firm's study conducted on Permethrin Cream 5% has been found unacceptable by the Division of Bioequivalence.

The firm should be informed of the above recommendation.

 /S/
Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 6/4/97

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

 /S/

Date: 6/4/97

Concur:  /S/
Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

Date: 6/6/97

MMakary/6-4-97 wp 74806S.697
cc: ANDA #74-806, original, HFD-650 (Director), HFD-658 (Makary),
Drug File, Division File.

MAR 31 1997

Permethrin Cream 5%
Topical
ANDA #74-806
Reviewer: Moheb H. Makary
WP 74806S.396

Barre-National Incorporated
Baltimore, MD
Submission Date:
February 16, 1996
June 15, 1996

Review of a Consultative Review of Clinical Bioequivalence Study

Introductions:

The Division of Bioequivalence requested a consultative review of data on the above drug as the first generic in which a generic permethrin drug product (Barre Permethrin 5% Permethrin Cream, [Apharma]) is compared to the innovator's (Elimite Permethrin 5% Cream) for the treatment of scabies infestation. The submission was sent to Division of Dermatologic and Dental Drug Products (HFD-540) for consult.

Human scabies infestation is usually spread by skin to skin contact, with a one month incubation period before allergic sensitization and itching occurs. Subsequent infestations produce immediate itching. Scabietic lesions are usually found on the interdigital webs, elbows, feet, genitalia, buttocks, and axilla. The burrow is the characteristic and diagnostic sign in adult infestation, although excoriations and secondary infection may make identification difficult. In scabies caused by animal mites, the characteristic burrows are seldom found. Pediatric scabies infestation tends to affect the palms, soles, head, neck and face, and frequently manifests erythematous papules/blisters as the predominant clinical sign. Burrows are demonstrable in only approximately 10% of pediatric cases.

The innovator product was approved by the agency in 1989 for the treatment of "infestation with *Sarcoptes scabiei* (scabies)", based upon the results of the four clinical trials.

Objective/Rationale

The objective of the study was to compare the safety and efficacy of two formulations of permethrin dermal cream in the treatment of scabies and possibly to establish bioequivalence of the two products.

Clinical Study:

One clinical trial involving 132 subjects was conducted in the (b)4 - Confidential and all subjects were native people. (Project No. 950804) 130 patients received treatment.

Study Design

This was a double blind, randomized, parallel study comparing an approved innovator drug product with a generic product without a placebo control. The patient's clinical signs and symptoms were evaluated on days 0, 1, 14, and 28 and collected on the case report forms.

Results:

Sponsors Outcomes

One hundred and thirty two patients were randomized into the trial. Two subjects (#16 and #86) did not receive treatment, so 130 were eligible for analysis. A total of 62 patients in each treatment arm of the sponsor's evaluable population completed the study at day 28 without significant protocol violations. The sponsor's criteria for completion of a visit is the presence of efficacy data. The efficacy data demonstrates the percentage of patient's considered to be "cured" on day 28. The results indicate that both the innovator and the comparator demonstrate 95.2% cure rates at day 28.

The Medical Officer's Outcomes

The Medical Officer removed two groups of subjects from the sponsor's evaluable population - those who did not present for day 14 visits, and those who demonstrated clinical signs of scabies on day 28 who were scored as "cured" by the sponsor. The Medical Officer scored more subjects in the failed category for each drug product. However, the sponsor's scores in each category are identical when comparing the outcomes for Elimite vs Barre, and the scores are again identical in each category when comparing the Medical Officer's outcomes for Elimite vs Barre. The sponsor's calculated cure rate for both drug products was 95.2%, while the Medical Officer's calculated cure rate for both drug products was 88.3%.

Safety outcomes

Subjects were monitored for safety via physical examination on days 1, 14, and 28. The investigators evaluated signs/symptoms which could be related to application of the drug product. Three subjects in the Barre group and 4 subjects in the Elimite group developed 'medical events' during the trial. These events included dermatophytosis, dermatobium hominis, molluscum contagiosum, diarrhea and dehydration, and chicken pox. No subject in either group experienced any signs or symptoms that was judged to be related to the application of topical 5% permethrin cream.

Review Comments by The Medical Officer

The data as presented demonstrates that the cure rate of Barre National 5% Permethrin Cream is equivalent to the cure rate of Elimite 5% Permethrin Cream in the treatment of human scabies infestation.

However, the following points should be clarified to ensure that the study was conducted in accordance with good clinical practices. These issues should be addressed prior to approval of the drug product.

1. Source documents are not available for this study. The reviewer requested source documents from the sponsor. In the amendment dated June 1996, the sponsor states that the case report forms are a substitute for the source document.

2. The study is conducted entirely in (b)4 - within a population which does not approximate the population which would use this drug in the US.

The (b)4 - Confidential Business have a high indigenous rate of scabies infection and have apparently been used as clinical subjects in many scabies trials, especially with this investigator. The demographics of infestation in this population do not match the target population in the US.

3. The sub-investigator making the clinical judgment of cured/not cured is not a physician.

(b)4 is not a physician, but has been a participant in previous trials submitted to the agency which were approved without discussion of his qualifications. The principal investigator is an M.D., but credentials were not provided for review.

4. The clinical study contains predominantly pediatric subjects. There are only 15 of 132 subjects who are over the age of 17. The majority of the patients are under the age of 6 years.

5. Pathognomonic signs of scabies (burrows) are not present on ANY adult subjects.

The clinical signs and symptoms tabulations plus many of the Case Report Forms were searched by this reviewer for documentation of burrows. The clinical trial is consistent with human scabies, but absence of burrows suggests that other mite infestations (animal scabies) are possible.

6. The sponsor may not have adequately demonstrated that mites were verified microscopically before patients were entered into the study.

Although a response to this question was received in the

amendment, the answer did not come from either the sponsor, the principal investigator, or the sub-investigator. As this is a critical aspect of the study, one of the principals should answer the question.

RECOMMENDATIONS

The Medical Officer recommends approval of this application provided that the conduct of the study has been shown to conform to good clinical practices. It is recommended that the Office of Generic Drugs consult with the Division of Scientific Investigations.

Recommended Regulatory Action:

The approval of Permethrin Cream 5% is pending upon acceptable inspection report from the Division of Scientific Investigations to ensure that the study was conducted in accordance with good clinical practices.

[Redacted] /S/

Moheb H Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

[Redacted] /S/

RM Date: 3/27/99

Concur: [Redacted] /S/

JN Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

3/22/97

MMakary/3-27-97/wp 74806S.396
cc: ANDA # 74-806, original, HFD-658 (Makary), Drug File.