

3. *Please provide the case report form for WHO Record #870781537 (in English) from the WHO database query submission (correspondence dated March 8, 1999).*

The WHO Record number changes when the report is updated. Therefore, the WHO record number requested #870781537 is not the same as the WHO Centre reference number on the attached printout; however, it is the same patient.

The Caveat Document is also attached, which explains the nature of the data collected in the WHO database. Please refer to ATTACHMENT 3-1.

4. *Please identify the country listed as Antilla under Foreign Marketing History (Vol. 1.57, pg. 065).*

Antilla consists of the following regions: Bahamas, Bermuda, Barbados, Jamaica, Haiti, Aruba and Curacao.

5. *Please clarify the study dates for Study 312. The study dates provided (Vol. 1.34, pg. 001) are 25 July 1994 - 26 March 1996. However, it is noted that subject #041/0218 had a post Week 16 visit dated 23 April 96 (Vol. 1.37, pg. 243).*

The study dates for Study 312 are 24 June 1994 (from the Demography data set - r100) through 4 December 1996 (from the Clinical Evaluation data set - r606). These dates were inadvertently incorrect in the report submitted in the NDA.

6. *Please provide:*

(a) *CRFs*

See ATTACHMENTS 6-1 and 6-2 for Study 312 and 313 respectively.

(b) *planimetric measurements, and,*

(c) *photographs (Baseline, Treatment Cure Visit [investigator's global assessment of clear, KOH-neg. & culture-neg.], and all Post-Treatment follow-up visits) for the following subjects:*

Study 312: 026/0104, 026/0116, 041/0218, 052/0402, 087/0926, & 052/0404.

Study 313: 028/1116, 036/1202, 036/1211, 036/1220, 036/1224, 044/1308, 047/1422, 063/1509, 088/1802 & 036/1219.

See ATTACHMENTS 6-3 and 6-4 for photographs from Study 312 and 313 respectively. The planimetric measurements and photographs for each patient are provided together. A tabular listing for the photographs and planimetric measurements for each subject is also provided.

Not all of the patients requested had planimetric measurements completed due to either failed Quality Assurance or not assessable time points (See Volume 6 Pages 2355 and 2401 for a table showing which patients have assessable time points available).

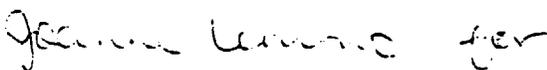
7. *(Requested via teleconference on August 3, 1999) Explanation of discrepancies in designation of target great toenail noted in Study 313, Vol. 1.46, Data Listing 5.2: Photography Results for Target Great Toenail ITT Subjects (e.g., patients 036/1202, 088/1802, and 044/1308). The same discrepancies were noted in Study 312 (Vol. 1.37) for patients 087/0926 and 052/0402.*

This request was addressed in a submission to the Division dated August 5, 1999.

Please note that a desk copy has been provided for Dr. Frank Cross.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

Encl.

cc: _____

S. Otto / R. Pooth, Hoechst Marion Rousell
A. Grignolo, PAREXEL International Corporation

APPEARS THIS WAY
ON ORIGINAL

ORIGIN

EM

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225



September 27 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMEN

RE: NDA 21-022
LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Dr. Alberto Grignolo on September 22, 1999, Sr. Vice President and General Manager, PAREXEL International, in which Mr. Cross requested the following information.

1) For the patients listed below, provide information on when they received non-lacquer topical ciclopirox product in relation to the myocardial enzyme signal (CKMB; this comment was based on information in the ISE and/or ISS):

Study 312:

Patient 052/0401
Patient 052/0412
Patient 087/0922
Patient 083/0711

Study 313

Patient 064/1604
Patient 066/1726

Please refer to Attachment 1.

2) Provide a listing (by Patient Number) of those patients who were considered a Treatment Cure in 312 and 313 at 48 Weeks and at Endpoint. Please clarify "Endpoint" means - is it 48 Weeks plus 2 weeks?

Endpoint is the last available non-missing assessment during treatment period of 48 weeks.

Please refer to Attachment 2.

3) For the Treatment Cure group, provide a history of the non-lacquer ciclopirox use in those patients. Be specific for each and every patient, whether assigned to active or to vehicle. This information is also relevant to Adverse Event monitoring.

Please refer to Attachment 3.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

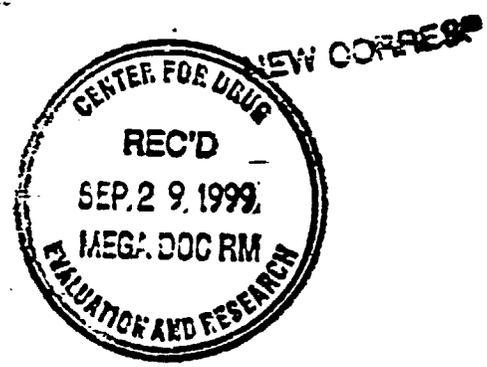
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NC

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223



September 28, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-022
LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Alicia Cabrelli, Regulatory Associate, PAREXEL International, on September 10, 1999, in which Mr. Cross requested the following information.

- 1) A copy of all the approved labeling for this NDA that is currently marketed in Europe and other countries, as well as the English translations.

The Sponsor is submitting the labeling for Germany, France and Austria because these countries are the leading markets for Ciclopirox Nail Lacquer 8%. These approved labeling are representative for all of the European Countries. The original country label, translation certificate and English translation for these 3 countries are provided. Please refer to Attachment 1.

The Standard Export Package Insert is the basis in all other non-US and non-European countries. This may be used either in English or in the local language of the country. Please refer to Attachment 2.

**APPEARS THIS WAY
ON ORIGINAL**

LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

NDA 21-022
Page Two

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225

ORIG AMENDMENT
BS

September 29, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-022
LOPROX® (ciclopirox) Nail Lacquer 8%
Sponsor Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made the facsimile from the Division to the Sponsor on September 24, 1999, regarding the tables from the Biostatistical review. With regard to this facsimile, the Sponsor hereby requests the following:

- 1) Is FDA definition for "Complete Cure" (on fax dated 9/24/99) same as HMR definition for "Treatment Cure"? Namely, it is for nail assessment with negative KOH, negative culture, and investigator's global score on target nail being "Cleared." Can FDA confirm the same definition was used for analyses shown on fax dated 9/24/99?
- 2) What is the FDA MITT definition? The MITT population identified by FDA is smaller than the PP population identified by HMR.
- 3) LOCF methodology: HMR performed the LOCF for each criteria and then performed the composite index. This methodology is clearly documented in ISE report section 3.2.2.4. It states that "for the endpoint analyses, individual components for the derived criterion could be from different visits. However, for mycological cure, the individual components (fungal culture and KOH) must be from the same visit." Is this convention being followed in the FDA review?

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,

Alicia Cabrelli

Alicia Cabrelli
Regulatory Affairs Associate

APPEARS THIS WAY
ON ORIGINAL

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225

September 3, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



ORIGINAL
NC

RE: NDA 21-022
LOPROX ® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the facsimile from FDA dated August 24, 1999.

The following information was requested in the facsimile:

1. For study 212, patient 030/103 — please provide:
 - a) Pregnancy outcome and
According to the NDA, (Vol. 1.98, pg. 233) the Case Record Form of patient 030/103 — states, "Subject does not meet protocol criteria- became pregnant- last menstrual cycle — Had her own pregnancy test on — " The date of this patient's visit was 3/17/89. Pregnancy outcome is not available at this time.
 - b) study arm (active or vehicle) assignment.
The patient was treated with active drug based on the randomization code. The drug decode "active" is given in the randomization list (Vol. 1.31, pgs. 074 & 075).
2. Location in the submission of the protocol, safety and efficacy results from the "open-label extension study" for patients enrolled in Study 211 and 212.
*Reference is made to the submission regarding Study 211 (Vol. 1.28, pg. 056) [It states, "...and an additional 12 patients (Centre 7) were enrolled into an open-label study extension."] and for Study 212 (Vol. 1.31, pg. 055)[It states "In addition, another patient (Centre 5, Loprox Lacquer 8% group) was enrolled into an open-label study extension and did not have a post treatment visit."]
There was no "open-label extension study" conducted for studies 211 and 212.
However, in each of the study protocols, there was an amendment implemented which*

stated (Vol. 1.64, pg. 026 for study 211 and Vol. 1.67, pg. 026 for study 212) "After 6 months of treatment, patients who show improvement of any treated nail may continue treatment with the active medication for an additional 6 months."

The additional 6 months data on these 13 patients was included in the ISS but not in the ISE. No separate analyses were conducted on the data for these 13 patients. Please advise if there are specific analyses that you would like to see conducted.

3. Please provide/correlate Center #s with investigators for Study 211 and 212.
See ATTACHMENT 1.

PARENEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Loprox® (Ciclopirox) Nail Lacquer 8% -- Study 211

Investigator/Address	Investigator Number	Center Number
C. Ralph Daniel, M.D. 514G East Woodrow Wilson Jackson, MS 39216	34	1
Vincent Falanga, M.D. University of Miami Department of Dermatology 1600 N.W. 10 th Avenue, Room 2089 Miami, FL 33101	29	2
Robert E. Kalb, M.D. SUNY at Buffalo School of Medicine Dept. of Dermatology 50 High Street, Suite 609 Buffalo, NY 14203	37	3
Ronald Savin, M.D. Adult & Adolescent Dermatology, P.C. 123 York Street New Haven, CT 06511	18	4
O. Fred Miller, II, M.D. Department of Dermatology Geisinger Medical Center North Academy Avenue Danville, PA 17821	42	5
Larry E. Millikan, M.D., F.A.C.P. Professor & Chairman Dept. of Dermatology Tulane University Medical Center 1430 Tulane Avenue New Orleans, LA 70112	43	6
Richard K. Scher, M.D. Dept. of Dermatology Columbia-Presbyterian Medical Ctr. - Rm. 750 161 Ft. Washington Avenue New York, NY 10032	46	7

Loprox® (Ciclopirox) Nail Lacquer 8% – Study 212

Investigator/Address	Investigator Number	Center Number
Raza Aly, PhD/Harry Roth, M.D. Department of Dermatology University of California, San Francisco San Francisco, CA 94143	30	1
Dennis E. Babel, PhD Edward A. Krull, M.D. Henry Ford Hospital 2799 West Grand Blvd. Detroit, MI 48202	33	2
Charles N. Ellis, M.D. Dept. of Dermatology University of Michigan Ann Arbor, MI 48104	35	3
Phillip Fleckman, M.D. Dept. of Dermatology, Room 14 School of Medicine University of Washington Seattle, WA 98195	36	4
James Kalivas, M.D. College of Medicine University of Kansas 39 th and Rainbow Kansas City, KS 66103	38	5
Manuel R. Morman, M.D. Rutherford Medical Plaza 17 Sylvan Street Rutherford, NJ 07070	41	7
Jerome L. Shupack, M.D. Department of Dermatology New York University Medical Center 560 First Avenue New York, NY 10016	47	8

PAREXEL

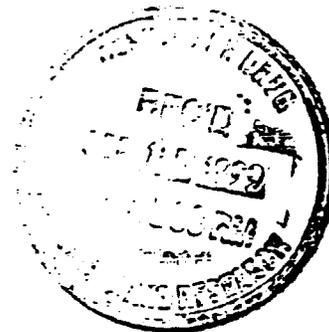
Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225

ORIGINAL

September 14, 1999

NEW CORRESP
A2

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-022
LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, dated September 9, 1999, in which Mr. Cross requested the following information.

1. A copy of the most recent labeling for the Loprox Nail Lacquer 8%.

No further updates referencing the labeling for Loprox Nail Lacquer 8% have been submitted to the Division since the December 18, 1998 submission of the NDA.

2. A copy of the patient package insert or medication guides, if available.

There is no patient package insert or medication guide available at this time.

3. A Carton Container Label with color 'mock up' of proposed name as trade name.

This will be submitted to the Division under separate cover.

4. For Study 111:

- a) Please obtain the urinary excretion of Ciclopirox (plus its glucuronide), as it was determined in the study.

Data on the urinary excretion are located in Vol. 1.4, page 239 of the NDA. For your convenience, a hard copy has been attached. Please refer to ATTACHMENT 1.

- b) Please provide information with supporting data in English about what percentage of the absorbed amount is excreted in the urine as the unchanged drug and its glucuronide in humans.

*Information on pharmacokinetics and metabolism can be found in the publication below. This publication in English is also included in the NDA (Vol. 1.62, page 045 - 083). Vol. 1.62, pgs. 044-100, of the NDA, contains a translation certificate, the English translation, and the German original publication.
Kellner H-M, Arnold CH, Christ OE, Eckert HG, Herok J, Hornke I, Rupp W. Study of the pharmacokinetics and biotransformation of the antimycotic ciclopirox olamine in animals and humans after topical and systemic use. Arzneimittel Forschung (Drug Research) 31 (11)8a:1337-1353 (1981). For your convenience, a hard copy of the English translation has been attached. Please refer to ATTACHMENT 2.*

5. In reference to the investigator's statement in Vol. 1.4, pgs. 252-254, it states that evaluations of some nails were indicated as "9" (not applicable). Does this mean that those nails were healthy nails without disease involvement? Please clarify.

Please be advised that "9" (not applicable) as noted in Vol. 1.4, pgs. 252-254, is defined that the respective nail was "not infected" at baseline.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

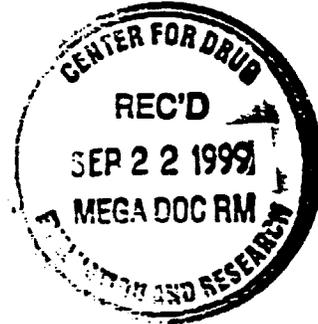
**APPEARS THIS WAY
ON ORIGINAL**

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

NEW CORRESP

NC



September 21, 1999

Frank H. Cross, Jr., M.A., CDR
Sr. Regulatory Management Officer and Commander
FDA; CDER
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

RE: NDA 21-022
Loprox® (ciclopirox) Nail Lacquer 8%

Dear Mr. Cross:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Further reference is made to the September 20, 1999 telephone conversation between Mr. Cross and Ms. Cabrelli. Mr. Cross requested a diskette copy (MS Word) regarding the labeling that was submitted in the NDA on December 18, 1998.

Included in this submission, please find a diskette (MS Word) containing the labeling information that was submitted in the NDA on December 18, 1998.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Please contact me at (610) 565-2622, ext. 2245 if you have any questions.

Sincerely,

Alicia Cabrelli
Alicia Cabrelli
Regulatory Affairs Associate

APPEARS THIS WAY
ON ORIGINAL

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BL

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225

September 27, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



WORLDWIDE AMENDMENT

RE: NDA 21-022
LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, dated September 9, 1999, in which Mr. Cross requested the following information. Please note Items 1-2, and 4 (a)(b)-5 of this request have been previously submitted to the Division on September 14, 1999.

3. A Carton Container Label with color "mock-up" of proposed name as trade name.

Please refer to Attachment 1.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,

A handwritten signature in cursive script that reads "Alicia Cabrelli".

Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

PAREXEL ORIGINAL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19065
Telephone: (610) 565-9400
Fax: (610) 565-5225

NEW CORRESP

October 27, 1999

NC



Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-022
LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on October 22, in which Mr. Cross requested the following information.

1. Photographs and associated planimetric diagrams (where applicable) for the following patients as slides for a slide projector:

Study 312:

- Patient 041/0218 Week 48
- Patient 052/0402 Post Week 12

Study 313:

- Patient 028/1116 Week 48
- Patient 036/1202 Week 48
- Patient 036/1211 Week 48
- Patient 036/1224 Post Week 12
- Patient 063/1509 Week 48

Please refer to attached slides. Also, the following patients did not have planimetric diagrams: Patient 041/0218, Patient 036/1224 and Patient 063/1509.

*These patients failed Quality Control analyses that were done prior to planimetry.
Some reasons for failed Quality Control checks may consist of the following:*

- *Technical adequacy marking of the distal groove*
- *Technical adequacy marking of the area of involvement*

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

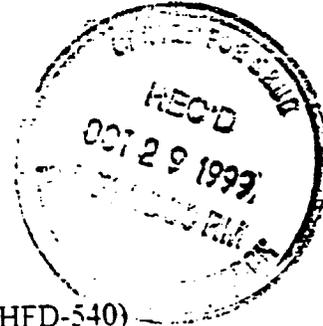
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Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19065
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Fax: (610) 565-5223

October 29, 1999

ORIG AMENDMENT



Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-022
LOPROX ® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on October 25, in which Mr. Cross requested the following information.

1. Photographs and associated planimetric diagrams (where applicable) for the following patients as slides for a slide projector:

Study 312:

- Patient 026/0104 Week 48
- Patient 026/0116 Week 48
- Patient 072/0511 Week 48
- Patient 087/0926 Week 48
- Patient 052/0404 Week 48

Study 313:

- Patient 036/1220 Week 48

Please refer to attached slides.

**APPEARS THIS WAY
ON ORIGINAL**

PARENEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

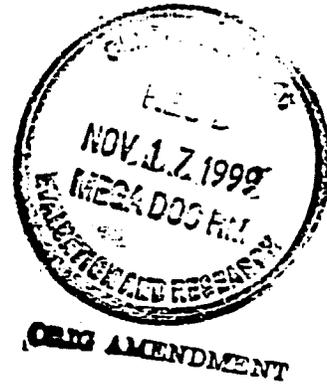
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PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

November 16, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



BL

RE: NDA 21-022
(ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on November 12, in which Mr. Cross requested the following information.

1. Patient Package Insert for (ciclopirox) Nail Lacquer 8%, based on the recommendations of the Advisory Committee Meeting on November 4, 1999.
Please refer to Attachment 1.
2. On August 31, 1999, PAREXEL International was informed that the Nomenclature Review Group did not approve _____
The new proposed drug name is "PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%". Expedited review is requested for this name change.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,

Alicia Cabrelli
Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PAREXEL

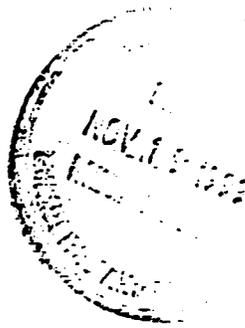
Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

ORIG AMENDMENT

BM

November 18, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-022
(ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on October 29, in which Mr. Cross requested the following information.

1. Photographs and associated planimetric diagrams (where applicable) for the following patients as slides for a slide projector:

Study 312:

- Patient 087/0926 Baseline

Study 313:

- Patient 047/1422 Baseline
- Patient 064/1618 Baseline

Please refer to attached slides.

Also, please be advised that these slides were previously submitted to Mr. Frank Cross, Sr. Regulatory Project Manager, on Tuesday, November 1, 1999 for his reference for the Advisory Committee Meeting.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,

Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

ORIG AMENDMENT

BC

November 19, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



**RE: NDA 21-022
(ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information**

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the Discipline Review Letter forwarded to Hoechst Marion Roussel, Inc. on September 13, 1999. The letter of September 13, 1999 also refers to the submission dated June 25, 1999.

Below are the deficiencies that were noted by the Division after a complete review of the chemistry section of the submission, as well as the Sponsor's response in *Italics*.



Redacted 1

pages of trade

secret and/or

confidential

commercial

information

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

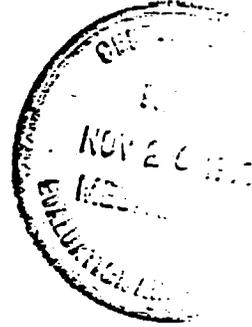
APPEARS THIS WAY
ON ORIGINAL

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225

November 24, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



BM

RE: NDA 21-022
(ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's telephone conversation with Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on November 17, and November 18, 1999, in which Mr. Cross requested the following information.

November 17, 1999

1. The number of geriatric patients enrolled in Studies 312 and 313.

The number of geriatric patients enrolled in Study 312 is 30.

The number of geriatric patients enrolled in Study 313 is 31.

Please be advised that these numbers are based on age calculation of >65.0. There are 6 patients listed below and on the referenced Attachment 1.

Study 312 Pt. 072/0512

Study 313 Pt. 028/1101

Study 313 Pt. 028/1119

Study 313 Pt. 063/1506

Study 313 Pt. 064/1628

Study 313 Pt. 066/1719

Please refer to Attachment 1.

2. Location in the NDA of the full report of the photoallergenicity and phototoxicity testing.

These studies were not done for the Ciclopirox Nail Lacquer 8% NDA. However, below is an outline of the chronological communication between the Division and the Sponsor that dates back to 1995

ORIGINAL

- A) *The End of Phase II Briefing Document, page 4, section "Issues and questions for discussion" states, "In addition, we would like FDA's concurrence that the dermatotoxicity program is unnecessary" and later in the text on page 32, it states, "We request a waiver of the battery of 4 topical dermatotoxicity tests based on previous dermatotoxicity testing of ciclopirox and ciclopirox olamine formulations, the innocuous nature of the vehicle, and the large numbers of patients who already have used ciclopirox nail lacquer for relatively long periods of time during clinical trials and through foreign post-marketing experience. ...neither ciclopirox nor ciclopirox olamine appear to have a potential to act as a contact sensitizer, contact photosensitizer, or to elicit phototoxic reactions. In addition, neither ciclopirox nor components of the vehicle exhibit significant absorption of light in the UVA range. ... The information on dermatotoxicity available at this point in time for ciclopirox nail lacquer is, in fact, greater than that which would be derived now from Phase I predictive tests. We would like concurrence from the Division that for this product, whose use is primarily limited to the nail plate, local safety is adequately documented by observations made during the lengthy clinical trials in progress or completed. Predictive tests, which will provide little additional information, therefore, need not be conducted. Please refer to Attachment 2.*
- B) *According to the available minutes (from the Sponsor) of the September 11, 1995 End of Phase 2 Meeting, "FDA is willing to consider — proposal for waiver of dermatotoxicity testing. ... With regard to phototoxicity testing, FDA would like to see the UV absorption spectrum for the drug..." This request was submitted by — to the Division on October 6, 1995. On page 5 & 6 of these minutes, — discusses dermatotoxicity. In the document it states, "... In addition the UV absorption spectrum of ciclopirox (please refer to the attached absorption curve) peaks at approximately 300 nm, well before the UVA range. The absorption spectrum would explain the absence of dermatotoxic reactions either reported in the literature, clinical trials, or dermatotoxic tests of photoallergenicity or phototoxicity, and should negate the need for further phototesting. ... We propose a waiver of the dermatotoxicity program for Loprox (ciclopirox) Nail Lacquer 8%, based on the amount of information already available for ciclopirox/ciclopirox olamine, the wide usage of this drug both in the USA and worldwide, and the inapplicability of the protocols to this formulation." Please refer to Attachment 3.*
- C) *On November 8, 1995, there was a teleconference between — and the Division. According to the Sponsor's minutes, Contact Sensitivity and Phototoxicity/Photosensitivity were discussed. Dr. Wilkin requested information on the phototoxicity protocol done in animals and summaries of clinical phototoxicity/photosensitization studies with any ciclopirox or ciclopirox olamine formulation. If studies seemed satisfactory, requirements for phototoxicity and photosensitivity may be waived. Please refer to Attachment 4.*
- D) *Photoallergenicity and Phototoxicity studies were submitted in the ciclopirox Gel, NDA 20-519.*
— *Study HOE296b 8/USA/122/-- (Phototoxicity study): Volume 1.26, page 183.*
— *Study HOE296b 8/USA/123/-- (Photoallergenicity study): Volume 1.27, page 1.*
Please refer to Attachment 5.
- E) *The pre-NDA meeting took place on August 18, 1997. The need for phototoxicity/photoallergenicity studies was not addressed at the pre-NDA meeting nor did the FDA minutes of the meeting address the need for such studies.*

In addition, we would like to mention that the results of long term exposure of Ciclopirox Nail lacquer up to 2 years in well controlled studies (312/313) and in a compassionate use study (320), gave no hint for concern in terms of phototoxicity or photoallergenicity.

If the FDA believes these studies must be conducted, HMR is willing to perform them as a Phase IV commitment.

November 18, 1999- Requests

1. Carton-Container in MS Word format on diskette.
Only the text can be converted into MS Word format. No further action required by the Sponsor. (Telephone contact report on November 22, 1999 between the Sponsor and Division).
2. Patient Instruction Sheets in MS Word format on diskette.
No further action required by the Sponsor. (Telephone contact report on November 22, 1999 between the Sponsor and Division).
3. Regarding the submission of PENLAC™. Mr. Cross understood where the "LAC" was derived from (Lacquer). However, he was interested in the significance of "PEN". He asked if this was used in Europe.
There is no significance to the PENLAC™ tradename and it is not used in Europe.
4. Was the formulation used in the clinical studies 211, 212, 312, and 313, was the formulation used the final to be marketed formulation? If so, where does it state in the NDA that it was the final to be marketed formulation?
It is confirmed that the composition of clinical batches 211, 212, 312, and 313 is identical with the composition of the future product to be marketed. Reference is made to NDA, Vol. 1.1, pages 004, 099 and 100.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

PAREXEL

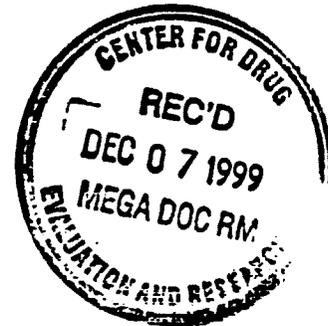
Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

December 6, 1999

NDA ORG AMENDMENT

BL

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-022
(ciclopirox) Nail Lacquer 8%
Response to FDA Draft Labeling

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Mr. Frank Cross's facsimile transmission on December 1, 1999 to Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, in which Mr. Cross requested the following information.

1. For your review/concurrence draft labeling for NDA 21-022, TRADENAME® NAIL LACQUER (ciclopirox) Topical Solution, 8%.
Please refer to Attachment 1.
The Sponsor has provided a side-by-side document comparison as well as a document that reflects clean draft text with "changes" incorporated into the labeling.
2. For your review/concurrence, draft carton/container labeling for NDA 21-022, TRADENAME® NAIL LACQUER (ciclopirox) Topical Solution, 8%.
The Sponsor concurs with the Division's changes.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,


Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

ORIGINAL

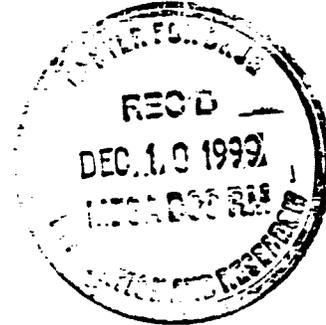
ORIGINAL
PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
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Fax: (610) 565-5223

ORIG AMENDMENT

BL

December 8, 1999



Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-022
(ciclopirox) Nail Lacquer 8%
Sponsor's Proposal to FDA Draft Labeling

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to Ms. Cabrelli's facsimile transmission on December 7, 1999 to Mr. Cross, in which the Sponsor requested the Division, to review the proposed labeling.

1. The Sponsor's proposed changes were to the Indications and Usage section, as well as the second table in the Clinical Trials section.
Please refer to ATTACHMENT 1.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,

Alicia Cabrelli
Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

DUPLICATE PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

ORIG AMENDMENT

FL

December 13, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-022
PENLAC™ Nail Lacquer (ciclopirox) Topical Solution, 8%
Sponsor's Draft Labeling

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the teleconference on December 7, 1999, between the Division and the Sponsor, where it was agreed that the Sponsor submits the proposed labeling to the Division for review/concurrence.

1. The Sponsor's draft labeling for NDA 21-022, PENLAC® NAIL LACQUER (ciclopirox) Topical Solution, 8%.

Please refer to ATTACHMENT 1.

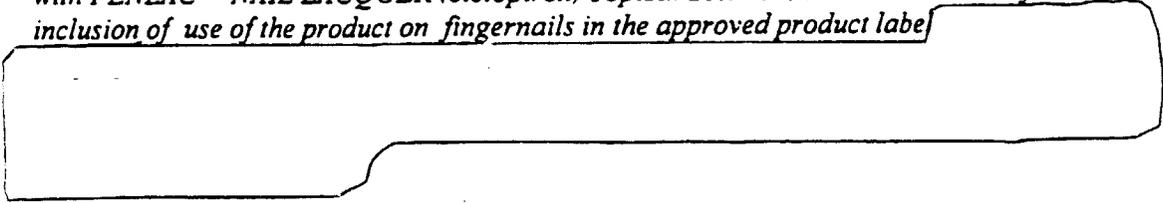
Changes that are made throughout the document are reflective of the discussions during the teleconference on December 7, 1999, between the Division and the Sponsor. Please see below for the following documents included in this attachment:

- *The Sponsor has provided a side-by-side document comparison that was faxed to the Division on December 9, 1999.*
- *Side-by-side comparison. However, the side-by-side comparison with Tradename® changed to PENLAC™ on the Sponsor side (but not in the FDA text on the left).*
- *Clean draft text with "changes" incorporated into the labeling which reflects the tradename PENLAC™.*
- *Lastly, included is the patient listing of the Week 12 post-treatment status for the 17 patients who were considered 'completely cured' at Week 48. This listing supports the numbers of the Week 12 post-treatment summary table in the attached labeling.*

2. Also, based on the agreements reached during the teleconference of December 7, the Sponsor proposes the following wording in reference to the Phase 4 commitment:

NDA 21-022
Response to Request for Information
December 13, 1999

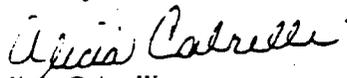
*phototoxicity and photoallergenicity studies
with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a condition for
inclusion of use of the product on fingernails in the approved product label*



PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

NDA ORIG AMENDMENT

BL

December 14, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-022
PENLAC™ Nail Lacquer (ciclopirox) Topical Solution, 8%
Sponsor's Carton/Bottle Label

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the request of Mr. Frank Cross on December 10, 1999 requesting the Sponsor's carton and bottle container label to the Division for review/concurrence.

1. The Sponsor's carton/bottle labeling for NDA 21-022, PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%.

Please refer to ATTACHMENT 1.

Please note that this was sent via facsimile to the Division on Friday, December 10, 1999.

However this was an incorrect version. The Sponsor sent to the Division via facsimile a corrected version on December 14, 1999. Included in this attachment are the following:

- *Corrected carton/bottle label version (faxed to the Division on December 14, 1999);*
- *Mark-up carton/bottle label version noting the corrections (faxed to the Division on December 14, 1999);*
- *Incorrect carton/bottle label version (faxed to the Division on December 10, 1999).*

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,

Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

ORIGINAL

PAREXEL

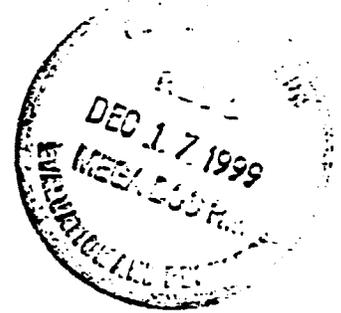
Rose Tree Corporate Center
1400 N. Providence Road, Suite 200C, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

ORIGINAL

December 15, 1999

NEW CORRESP

NC



Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-022
PENLACT™ Nail Lacquer (ciclopirox) Topical Solution, 8%
Sponsor's Request for Labeling Consideration

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the teleconference between the Sponsor and the Division on December 7, 1999.

During this teleconference, you had voiced concern about the concomitant use of ciclopirox nail lacquer with oral antifungal agents. Consequently, the FDA proposed wording in the "Interactions" section of the label that recommends that ciclopirox not be used concomitantly with those drugs; and proposed similar wording for inclusion in the "Indications and Usage" section.

HMR understands your concern regarding the lack of data on potential interactions between ciclopirox and oral antifungal agents. Specifically, you indicated that it is theoretically possible that coadministration of ciclopirox with an oral antifungal drug could alter (for the worse) the efficacy profile of the oral drug for treatment of onychomycosis. You cited as an analogy the antagonism of a bacteriostatic drug (a tetracycline) with a bactericidal drug (a penicillin). You indicated that you did not have a concern about any potential effects on safety resulting from concomitant fungal treatments. Your concern was that any erosion of the efficacy of the oral agent might impact that oral drug's overall efficacy-to-risk ratio.

As in the example mentioned by yourself, when two antimicrobial therapies are co-administered they may have mutually antagonistic effects. Conversely, combination therapy may result in additive, or even synergistic effects. Antimicrobial activity of drug combinations may be assessed by a variety of *in vitro* techniques, including dilution testing (assessing effects on MICs) and quantitation of rates of cidal activity.

To date there are no data suggesting either antagonistic or synergistic effects of ciclopirox with other antifungal agents; to our knowledge no such studies have been conducted. HMR proposes to undertake *in vitro* studies to assess the potential effects of ciclopirox on the antifungal activity of terbinafine and of itraconazole. HMR understands, from the FDA's previous comments on the labeling, the concern of the Agency relative to the standardization of test methods. HMR proposes to undertake these studies with the concurrence of the Agency that the test methods would be suitable to address the interaction issue.

In the context of a Phase 4 commitment to conduct *in vitro* studies to determine any effects of ciclopirox on terbinafine and on itraconazole activity, HMR requests that the comments regarding concomitant therapy in the "Antifungal Drug Interactions" section be amended to: "...is not recommended, at this time." And that the reference to concomitant therapy (bullet point number 1: "The concomitant use...") in the "Indications and Usage" section be deleted.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5225

ORIGINAL

~~ORIG~~ AMENDMENT

BL

December 16, 1999



Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20857

RE: NDA 21-022
PENLAC™ Nail Lacquer (ciclopirox) Topical Solution, 8%
Sponsor's Response to Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the telephone conversation between Mr. Frank Cross, and Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on December 15, 1999, and the teleconference between the Division and Sponsor on December 16, 1999.

Requests from December 15, 1999

1. Confirmation of the Phase IV commitment can be completed within 1 year from approval. *The following was submitted via facsimile to the Division on December 9, 1999 and officially submitted to the Division on December 13, 1999.*
HMR commits within one year of approval to the post-approval conduct of phototoxicity and photoallergenicity studies with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a condition for inclusion of use of the product on fingernails in the approved product label (as indicated in the proposed draft, dated Dec. 9, 1999). HMR will submit the study protocols to the Division for their review prior to the conduct of said studies, to assure that the studies fully serve the needs of the Sponsor and the Agency with regard to the use of the product for treatment of fingernails.
2. Confirmation that HMR can commit to submitting the final study report to the Division one-year from approval regarding the Phase 4 commitment from the December 9, 1999 facsimile and the official submission of December 13, 1999.
The Sponsor agrees to conduct the above Phase 4 studies and submit final study reports to the Division within one year of NDA approval. The Sponsor will submit the relevant protocols to the Division for review and comment in advance. The timing of submission of the final study reports presumes that the Division will review and comment on the protocols in a timely manner (e.g. 4-6 weeks after receiving them).

NDA 21-022
December 16, 1999

3. The Division recommends revised carton and bottle label.

Please see Attachment 1.

The changes are as follows:

1. *Important: This package is not child resistant -- has been added beneath the Warning statement on the carton.*
2. *Reference to Hoechst Marion Roussel on the front, side, and top panels has been deleted.*
3. *The Mfd. by and Mfd. for text has been revised to show appropriate Aventis text. The street address for Aventis, Kansas City has been added per the regulations because Aventis is not listed in the current telephone directory.*
4. *Marketed by DERMIK LABORATORIES, INC. text has been added to the carton.*
5. *The bottle label has been revised to show the Aventis name.*

Request from December 16, 1999:

1. Per the teleconference, it was recommended by the Sponsor to correct the information regarding the Mfd by, Mfd for, Marketed by text, which appears on the last page of the PI.

Please see Attachment 2.

Marketed by DERMIK LABORATORIES, INC. text has been added to the package insert.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc. (effective today, Aventis).

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PAREXEL International Corporation

**Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000
Media, PA 19063-2043
Telephone: 610-565-2622
Fax: 610-565-5866**

**CONFIDENTIAL
FAX TRANSMITTAL FORM**

ATTENTION: Frank Cross, Sr. Regulatory Project Manager
U.S. Food and Drug Administration

FAX #: 301-827-2075/2091

FROM: Alicia Cabrelli

DATE: December 17, 1999

OF PAGES:
(Including Cover)

THE INFORMATION IN THIS FACSIMILE COMMUNICATION IS INTENDED SOLELY FOR THE USE OF THE INDIVIDUAL NAMED ABOVE. IF YOU ARE NOT THE INTENDED RECIPIENT, OR AN EMPLOYEE OR AGENT OF THE RECIPIENT WHO IS RESPONSIBLE FOR DELIVERING THIS COMMUNICATION TO THE INTENDED RECIPIENT, YOU ARE HEREBY NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR PHOTOCOPYING OF THIS COMMUNICATION OR THE INFORMATION CONTAINED IN THIS COMMUNICATION IS STRICTLY PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION IN ERROR, PLEASE IMMEDIATELY NOTIFY THE SENDER BY TELEPHONE (COLLECT) SO THAT THE SENDER MAY ARRANGE FOR RETURN OF THE ORIGINAL COMMUNICATION. THANK YOU.

**NOTES: Re: NDA 21-022
PENLAC™ Nail Lacquer (ciclopirox) Topical Solution, 8%
Sponsor's Response to Draft Approval Letter and Labeling**

Dear Mr. Cross:

On behalf of the Sponsor, Aventis, please acknowledge this facsimile as acceptance of the Approval Letter and Labeling that was faxed to the Sponsor, on December 16, 1999.

If you have any further questions, please feel free to contact me at 610-565-2622, ext. 2245.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate

**APPEARS THIS WAY
ON ORIGINAL**

PAREXEL International Corporation

**Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000
Media, PA 19063-2043
Telephone: 610-565-2622
Fax: 610-565-5866**

**CONFIDENTIAL
FAX TRANSMITTAL FORM**

ATTENTION: Frank Cross, Sr. Regulatory Project Manager
U.S. Food and Drug Administration

FAX #: 301-827-2075/2091

FROM: Alicia Cabrelli

DATE December 16, 1999

OF PAGES:
(Including Cover)

4

THE INFORMATION IN THIS FACSIMILE COMMUNICATION IS INTENDED SOLELY FOR THE USE OF THE INDIVIDUAL NAMED ABOVE. IF YOU ARE NOT THE INTENDED RECIPIENT, OR AN EMPLOYEE OR AGENT OF THE RECIPIENT WHO IS RESPONSIBLE FOR DELIVERING THIS COMMUNICATION TO THE INTENDED RECIPIENT, YOU ARE HEREBY NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR PHOTOCOPYING OF THIS COMMUNICATION OR THE INFORMATION CONTAINED IN THIS COMMUNICATION IS STRICTLY PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION IN ERROR, PLEASE IMMEDIATELY NOTIFY THE SENDER BY TELEPHONE (COLLECT) SO THAT THE SENDER MAY ARRANGE FOR RETURN OF THE ORIGINAL COMMUNICATION. THANK YOU.

**NOTES: Re: NDA 21-022
PENLAC™ Nail Lacquer (ciclopirox) Topical Solution, 8%**

Dear Mr Cross:

Attached for your review is the Sponsor's letter referencing the Division's requests from December 15th and December 16th in which the following are addressed:

1. Phase 4 commitments
2. Revised carton label
3. Addition of the "Mkt by" statement for on the last page of the PI.

If you have any further questions, please feel free to contact me at 610-565-2622, ext. 2245.

Sincerely,



Alicia Cabrelli
Regulatory Associate

**APPEARS THIS WAY
ON ORIGINAL**



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: August 4, 1999 Number of Pages (including cover sheet) - 2

TO: Tracie Parker, B.S., Manager, Regulatory Affairs
COMPANY: Paraxel International Corporation
FAX #: 610-565-5223

MESSAGE: With regard to NDA 21-022, Loprox (ciclopirox) Nail Lacquer, 8%, we have the following request:

- 1) Location in the NDA submission of a description of the "computerized photoplanimetric method" used to determine percent involvement for Studies 312 and 313.
- 2) Location of Treatment Emergent Adverse Events Table (for all subjects)/rates by body system irrespective of relationship to study drug for Study 211 and Study 212. Please provide a copy in MS Word format.
- 3) Please provide the case report for WHO Record #870781537 (in English) from the WHO database query submission (correspondence dated March 8, 1999).
- 4) Please identify the country listed as Antilla under Foreign Marketing History (Vol. 1.57, pg. 064).
- 5) Please clarify the study dates for Study 312. The study dates provided (Vol. 1.34, pg. 001) are 25 July 1994 - 26 March 1996. However, it is noted that subject #041/0218 had a Post Week 16 visit dated 23 April 96 (Vol. 1.37, pg. 243).
- 6) Please provide:
 - (a) CRFs,
 - (b) planimetric measurements), and

- (c) photographs (Baseline, Treatment Cure Visit [investigator's global assessment of clear, KOH-neg. & culture-neg.], and all Post-Treatment follow-ups visits) for the following subjects:

Study 312- 026/0104, 026/0116, 041/0218, 052/0402, 087/0926, & 052/0404.

Study 313- 028/1116, 036/1202, 036/1211, 036/1220, 036/1224, 044/1308, 047/1422, 063/1509, 088/1802, & 036/1219.

- 7) (Requested via T-Con on 8/3/99) Explanation of discrepancies in designation of target great toenail noted in Study 313, Vol. 1.46, Data Listing 5.2: Photography Results for Target Great Toenail ITT Subjects (e.g., patients 036/1202, 088/1802, and 044/1308). The same discrepancies were noted in Study 312 (Vol. 1.37) for patients 087/0926 and 052/0402.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

COMPANY: Paraxel International Corporation

FAX #: 610-565-5223

MESSAGE: With regard to NDA 21-022, Loprox (ciclopirox) Nail Lacquer, 8%, we have the following request:

- 1) Location in the NDA submission of a description of the "computerized photoplanimetric method" used to determine percent involvement for Studies 312 and 313.
- 2) Location of Treatment Emergent Adverse Events Table (for all subjects)/rates by body system irrespective of relationship to study drug for Study 211 and Study 212. Please provide a copy in MS Word format.
- 3) Please provide the case report for WHO Record #870781537 (in English) from the WHO database query submission (correspondence dated March 8, 1999).
- 4) Please identify the country listed as Antilla under Foreign Marketing History (Vol. 1.57, pg. 064).
- 5) Please clarify the study dates for Study 312. The study dates provided (Vol. 1.34, pg. 001) are 25 July 1994 - 26 March 1996. However, it is noted that subject #041/0218 had a Post Week 16 visit dated 23 April 96 (Vol. 1.37, pg. 243).
- 6) Please provide:
 - (a) CRFs,
 - (b) planimetric measurements), and

APPEARS THIS WAY
ON ORIGINAL

08/04 11:27	00'34"	6105655223	002/002	OK		10002
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MESSAGE CONFIRMATION



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: August 24, 1999 Number of Pages (including cover sheet) - 1

TO: Alicia Cabrelli, Regulatory Affairs Associate
COMPANY: Paraxel International Corporation
FAX #: 610-565-5866

MESSAGE: With regard to NDA 21-022, Loprox (ciclopirox) Nail Lacquer, 8%, we have the following requests:

1. For Study 212, patient 030/103 _____, please provide:
 - a. pregnancy outcome and
 - b. study arm (active or vehicle) assignment.
2. Location in the submission of the protocol, safety and efficacy results from the "open-label extension study" for patients enrolled in Study 211 and 212.
3. Please provide/correlate Center #s with investigators for Study 211 and 212.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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COMPANY: Paraxel International Corporation
 FAX #: 610-565-5866

MESSAGE: With regard to NDA 21-022, Loprox (ciclopirox) Nail Lacquer, 8%, we have the following requests:

1. For Study 212, patient 030/103 — \, please provide:
 - a. pregnancy outcome and
 - b. study arm (active or vehicle) assignment.
2. Location in the submission of the protocol, safety and efficacy results from the "open-label extension study" for patients enrolled in Study 211 and 212.
3. Please provide/correlate Center #s with investigators for Study 211 and 212.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
 TITLE: Senior Regulatory Management Officer
 PHONE #: 301-827-2063
 FAX #: 301-827-2075/2091

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08/24/99 16:43

MESSAGE CONFIRMATION



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 24, 1999 Number of Pages (including cover sheet) - 2

TO: Alicia Cabrelli, Regulatory Affairs Associate
COMPANY: Paraxel International Corporation
FAX #: 610-565-5866

MESSAGE: With regard to NDA 21-022, Loprox (ciclopirox) Nail Lacquer, 8%, and to our conversation on September 23, 1999, attached to this facsimile transmission are the tables from the Biostatistical review of the aforementioned NDA.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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NDA 21002 Loprox Nail Lacquer

Study 312 Complete Cure MITT Population:

	48	Post-treatment		
		12	24	
	LOCF-	week	week	
	(48 wks)	(+ LOCF)	(+ LOCF)	
Loprox cure	3	3	1	1
N	70	80	78	79
%	4.3	3.8	1.3	1.3
Vehicle cure	0	0	0	0
N	64	80	80	80
%	0.0	0.0	0.0	0.0
CMH p-value	0.075	0.059	0.254	0.277
Fisher p-value	0.246	0.245	0.494	0.497

ITT Population:

Loprox cure	4	4	2	2
N	91	112	110	111
%	4.4	3.6	1.8	1.8
Vehicle cure	1	1	1	1
N	83	110	110	110
%	1.2	0.9	0.9	0.9
CMH p-value	0.231	0.184	0.559	0.573
Fisher p-value	0.370	0.369	1.000	1.000

Study 313 Complete Cure MITT Population:

	48	Post-treatment		
		12	24	
	LOCF-	week	week	
	(48 wks)	(+ LOCF)	(+ LOCF)	
Loprox cure	5	5	1	0
N	75	84	83	79
%	6.7	6.0	1.2	1.2
Vehicle cure	0	0	0	0
N	75	92	92	92
%	0.0	0.0	0.0	0.0
CMH p-value	0.019	0.012	0.254	NA
Fisher p-value	0.058	0.023	0.477	NA

ITT Population:

Loprox cure	8	10	3	2
N	95	118	115	111
%	8.4	8.5	3.5	2.7
Vehicle cure	0	0	0	0
N	85	117	117	117
%	0.0	0.0	0.0	0.0
CMH p-value	0.004	0.001	0.066	0.134
Fisher p-value	0.007	0.002	0.122	0.240

**APPEARS THIS WAY
ON ORIGINAL**

COMPANY: Paraxel International Corporation

FAX #: 610-565-5866

MESSAGE: With regard to NDA 21-022, Loprox (ciclopirox) Nail Lacquer, 8%, and to our conversation on September 23, 1999, attached to this facsimile transmission are the tables from the Biostatistical review of the aforementioned NDA.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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09/24/99 12:03

MESSAGE CONFIRMATION



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 1, 1999 Number of Pages (including cover sheet) - 14

TO: Alicia Cabrelli, Regulatory Affairs Associate
COMPANY: Paraxel International Corporation
FAX #: 610-565-5866

MESSAGE: For your review/concurrence please find attached to this facsimile transmission
draft labeling for NDA 21-022, TRADENAME® NAIL LACQUER (ciclopirox)
Topical Solution, 8 %

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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ON ORIGINAL**

13 Page(s) Redacted

Draft

Labeling

COMPANY: Paraxel International Corporation

FAX #: 610-565-5866

MESSAGE: For your review/concurrence please find attached to this facsimile transmission draft labeling for NDA 21-022, TRADENAME[®] NAIL LACQUER (clonidine) Topical Solution, 8 %

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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ESSF SE CONFIRMATION



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 1, 1999 Number of Pages (including cover sheet) - 3

TO: Alicia Cabrelli, Regulatory Affairs Associate
COMPANY: Paraxel International Corporation
FAX #: 610-565-5866

MESSAGE: For your review/concurrence please find attached to this facsimile transmission draft carton/container labeling for NDA 21-022, **TRADENAME[®] NAIL LACQUER** (ciclopirox) Topical Solution, 8 %.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 6, 1999
Number of Pages (including cover sheet) - 16

TO: Alicia Cabrelli, Regulatory Affairs Associate
COMPANY: Paraxel International Corporation
FAX #: 610-565-5866

MESSAGE: For your review/concurrence please find attached to this facsimile transmission draft labeling for NDA 21-022, **TRADENAME® NAIL LACQUER (ciclopirox)** Topical Solution, 8 %.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

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Draft

Labeling

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

December 16, 1999

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20857

RE: NDA 21-022
PENLAC™ Nail Lacquer (ciclopirox) Topical Solution, 8%
Sponsor's Response to Request for Information

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. Additional reference is made to the telephone conversation between Mr. Frank Cross, and Ms. Alicia Cabrelli, Regulatory Affairs Associate at PAREXEL International, on December 15, 1999, and the teleconference between the Division and Sponsor on December 16, 1999.

Requests from December 15, 1999

1. Confirmation of the Phase IV commitment can be completed within 1 year from approval. *The following was submitted via facsimile to the Division on December 9, 1999 and officially submitted to the Division on December 13, 1999. HMR commits within one year of approval to the post-approval conduct of phototoxicity and photoallergenicity studies with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a condition for inclusion of use of the product on fingernails in the approved product label (as indicated in the proposed draft, dated Dec. 9, 1999). HMR will submit the study protocols to the Division for their review prior to the conduct of said studies, to assure that the studies fully serve the needs of the Sponsor and the Agency with regard to the use of the product for treatment of fingernails.*
2. Confirmation that HMR can commit to submitting the final study report to the Division one-year from approval regarding the Phase 4 commitment from the December 9, 1999 facsimile and the official submission of December 13, 1999. *The Sponsor agrees to conduct the above Phase 4 studies and submit final study reports to the Division within one year of NDA approval. The Sponsor will submit the relevant protocols to the Division for review and comment in advance. The timing of submission of the final study reports presumes that the Division will review and comment on the protocols, in a timely manner (e.g. 4-6 weeks after receiving them).*

3. The Division recommends revised carton and bottle label.

Please see Attachment 1.

The changes are as follows:

- 1. Important: This package is not child resistant -- has been added beneath the Warning statement on the carton.*
- 2. Reference to Hoechst Marion Roussel on the front, side, and top panels has been deleted.*
- 3. The Mfd. by and Mfd. for text has been revised to show appropriate Aventis text. The street address for Aventis, Kansas City has been added per the regulations because Aventis is not listed in the current telephone directory.*
- 4. Marketed by DERMIK LABORATORIES, INC. text has been added to the carton.*
- 5. The bottle label has been revised to show the Aventis name.*

Request from December 16, 1999:

1. Per the teleconference, it was recommended by the Sponsor to correct the information regarding the Mfd by, Mfd for, Marketed by text, which appears on the last page of the PI.
Please see Attachment 2.
Marketed by DERMIK LABORATORIES, INC. text has been added to the package insert.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc. (effective today, Aventis).

Thank you for your attention. Please contact me at (610) 565-2622, extension 2245 if you have any questions.

Sincerely,



Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

2 Page(s) Redacted

Draft

Labeling

BEST POSSIBLE COPY

PAREXEL International Corporation

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000
Media, PA 19063-2043
Telephone: 610-565-2622
Fax: 610-565-5866

**CONFIDENTIAL
FAX TRANSMITTAL FORM**

ATTENTION: Frank Cross, M.A., CDR
Senior Regulatory Management Officer

COMPANY: U.S. Food and Drug Administration

FAX #: 301-827-2075

FROM: Tracie Parker

DATE: September 1, 1998

OF PAGES: 3
(Including Cover)

THE INFORMATION IN THIS FACSIMILE COMMUNICATION IS INTENDED SOLELY FOR THE USE OF THE INDIVIDUAL NAMED ABOVE. IF YOU ARE NOT THE INTENDED RECIPIENT OR AN EMPLOYEE OR AGENT OF THE RECIPIENT WHO IS RESPONSIBLE FOR DELIVERING THIS COMMUNICATION TO THE INTENDED RECIPIENT, YOU ARE HEREBY NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR PHOTOCOPYING OF THIS COMMUNICATION OR THE INFORMATION CONTAINED IN THIS COMMUNICATION IS STRICTLY PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION IN ERROR, PLEASE IMMEDIATELY NOTIFY THE SENDER BY TELEPHONE (COLLECT) SO THAT THE SENDER MAY ARRANGE FOR RETURN OF THE ORIGINAL COMMUNICATION. THANK YOU.

INFORMAL FAX

**RE: Loprox® (ciclopirox) Nail Lacquer 8%
NDA 21-022**

Dear Frank:

In preparation for the teleconference scheduled on Wed. Sept. 2 at 2:00 pm with yourself and Division statisticians to discuss their requirements for electronic submission of data for this NDA, the following lists what FDA will be receiving electronically from PAREXEL International, on behalf of Hoechst Marion Roussel, Inc., for the Loprox Nail Lacquer NDA:

DATASETS for the following Individual studies:

Study 211: A Double-Blind Study of the Safety and Efficacy of Ciclopirox (Loprox) Nail Lacquer 8% Versus its Lacquer Vehicle in Patients With Dermatophytic Onychomycosis of the Fingernails

Study 212: A Double-Blind Study of the Safety and Efficacy of Ciclopirox (Loprox) Nail Lacquer 8% Versus its Lacquer Vehicle in Patients With Dermatophytic Onychomycosis of the Fingernails

BEST POSSIBLE COPY

Study 312: A Double-Blind Study of the Safety and Efficacy of Ciclopirox (HOE 296NL) Nail Lacquer 8% Versus its Lacquer Vehicle in Patients With Distal Subungual Tinea Unguim of the Toenails

Study 313: A Double-Blind Study of the Safety and Efficacy of Ciclopirox (HOE 296NL) Nail Lacquer 8% Versus its Lacquer Vehicle in Patients With Distal Subungual Tinea Unguim of the Toenails

Study 320: An Open-Label Study of Ciclopirox (HOE 296NL) Nail Lacquer 8% in Patients With Distal Subungual Tinea Unguim of the Toenails

Study 111A: An Open Label Study to Determine the Safety, Efficacy and Systemic Absorption of Ciclopirox (Loprox) Nail Lacquer 8% in patients With Dermatophytic Onychomycoses of the Finger Nails

Study 1003: Repeated Insult Patch Study to Assess the Irritation and Sensitization Potential of Topically Applied Loprox Nail Lacquer 8%

Each of these studies will contain Raw data as well as Analysis datasets. The Analysis datasets contain any calculated data necessary for the creation of statistical output.

DATASETS for Integrated Databases:

ISS
ISE

These databases will be comprised of Analysis datasets created from the individual studies.

We would like to obtain confirmation during our teleconference tomorrow that the above information submitted electronically on to a single CD-ROM will suffice.

We would also like to confirm at tomorrow's teleconference that SAS version 6.09, which PAREXEL International uses on a VMS platform not Windows, is compatible with SAS version 6.12 used by the Division. Datasets created in SAS version 6.09 are compatible with SAS version 6.12.

The meeting attendees from our end will be follows:

PAREXEL International

Irving Dark -- Manager, Statistical Programming
Alberto Grignolo -- Senior Vice President, Worldwide Regulatory Affairs
Elaine Hoffer-- Sr. Programmer
Tracie Parker-- Sr. Regulatory Associate

Hoechst Marion Roussel, Inc.

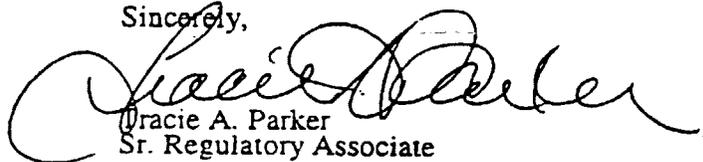
Michael French -- Manager, Regulatory Affairs

Loprox® (ciclopirox) Nail Lacquer 8%
NDA 21-022
Page 3 of 3

We look forward to this discussion with you and your colleagues, and to submitting the NDA.

We will contact you at 2:10 pm at 301-827-2094.

Sincerely,



Gracie A. Parker
Sr. Regulatory Associate

APPEARS THIS WAY
ON ORIGINAL