CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-022

CORRESPONDENCE

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 DRUG ...

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

Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	DECEMBER 6, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
(816) 966-5000	(816) 966-6790
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	**AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE**
10236 Marion Park Drive Kansas City, MO 64137-1405	PAREXEL International Corporation 195 West Street Waltham, MA 02154 (781) 466-8833

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-022

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ciclopirox nail lacquer 8%	LOPROX
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	**CODE NAME *(If any)***
	HOE 296

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
nail lacquer	8%	topical

(PROPOSED) INDICATION(S) FOR USE:
for the topical treatment of mild to moderate onychomycosis without lunula involvement due to Trichophyton rubrum. It is indicated for the treatment of fingernails and toenails.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
RESPONSE TO FDA'S DRAFT LABELING

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attached

91 Page(s) Redacted

Draft

Labeling

ORIGINAL

PAREXEL

ORIG AMENDMENT

BL

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1400 N. Providence Road, Suite 2000, Media, PA 19063
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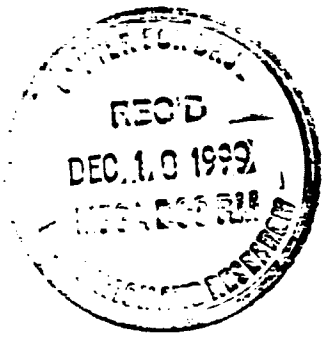

December 8, 1999

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

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NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	December 8, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(816) 966-5000	(816) 966-6790

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
10236 Marion Park Drive
Kansas City, MO 64137-1405

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
PAREXEL International Corporation
195 West Street
Waltham, MA 02154
(781) 466-8833

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-022

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ciclopirox nail lacquer 8%	LOPROX

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
	HOE 296

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
nail lacquer	8%	topical

(PROPOSED) INDICATION(S) FOR USE:
for the topical treatment of mild to moderate onychomycosis without lunula involvement due to Trichophyton rubrum. It is indicated for the treatment of fingernails and toenails.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Sponsor's Response to FDA's Draft Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attached

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Sponsor's Response to FDA's Draft Labeling

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
A. Grignolo for A. Grignolo	Alberto Grignolo, Ph.D., Sr. Vice President and General Manager, Worldwide Regulatory Affairs	12/8/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
195 West Street Waltham, MA 02154	(781) 466-8833

Please DO NOT RETURN this form to this address.

3 Page(s) Redacted

Draft

Labeling

DUPLICATE

PAREXEL

ORIG AMENDMENT

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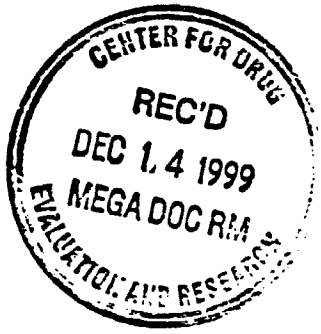
Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223



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:

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	December 13, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(816) 966-5000	(816) 966-6790

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
10236 Marion Park Drive
Kansas City, MO 64137-1405

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PAREXEL International Corporation
195 West Street
Waltham, MA 02154
(781) 466-8833

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-022

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ciclopirox nail lacquer 8%	LOPROX

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* HOE 296

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
nail lacquer	8%	topical

(PROPOSED) INDICATION(S) FOR USE
for the topical treatment of mild to moderate onychomycosis without lunula involvement due to Trichophyton rubrum. It is indicated for the treatment of fingernails and toenails.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Sponsor's Draft Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attached

24 **Page(s) Redacted**

Draft

Labeling

PAREXEL

Rose Tree Corporate Center
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Telephone: (610) 565-9400
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NDA ORIG AMENDMENT

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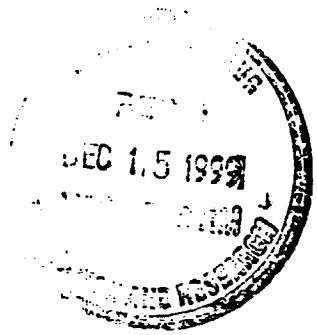

December 14, 1999

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

Alicia Cabrelli
Regulatory Affairs Associate
Worldwide Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

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Hoechst Marion Roussel, Inc.	December 14, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
(816) 966-5000	(816) 966-6790

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
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PAREXEL International Corporation
195 West Street
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PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-022

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ciclopirox nail lacquer 8%	LOPROX

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*: HOE 296

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
nail lacquer	8%	topical

(PROPOSED) INDICATION(S) FOR USE:
for the topical treatment of mild to moderate onychomycosis without lunula involvement due to Trichophyton rubrum. It is indicated for the treatment of fingernails and toenails.

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☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Sponsor's carton/bottle label

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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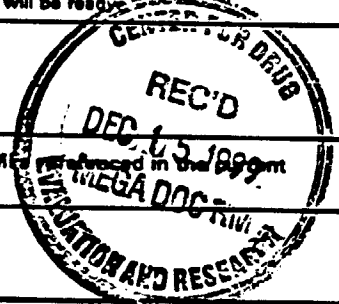
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attached



FORM FDA 356h (6/97)

3 **Page(s) Redacted**

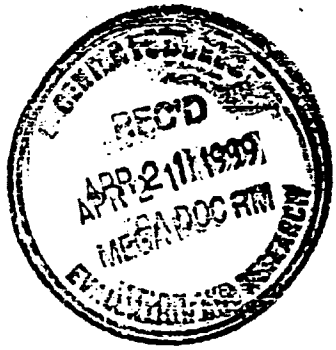
Draft

Labeling

ORIGINAL

PAREXEL

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



April 20, 1999

Jonathan Wilkin, MD
Director
CDER
U.S. Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD-540)
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

RE: NDA 21-022
Loprox® (ciclopirox) Nail Lacquer 8%
NDA Amendment: Item 9 – Safety Update

Dear Dr. Wilkin:

PAREXEL International Corporation, on behalf of Hoechst Marion Roussel, Inc., hereby amends the above referenced NDA with two copies of Item 9, Safety Update (120 days).

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	April 20, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(816) 966-5000	(816) 966-6790

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
10236 Marion Park Drive
Kansas City, MO 64137-1405

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
PAREXEL International Corporation
195 West Street
Waltham, MA 02154
(781) 466-8833

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-022

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ciclopirox nail lacquer 8%	LOPROX

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*: HOE 296

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
nail lacquer	8%	topical

(PROPOSED) INDICATION(S) FOR USE:
for the topical treatment of mild to moderate onychomycosis without lunula involvement due to Trichophyton rubrum. It is indicated for the treatment of fingernails and toenails.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
120-Day Safety Update

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attached

APR 21 1999
EVALUATION AND RE

EF

Electronic Mail Message

Date: 12/6/99 2:27:14 PM
From: Dennis Bashaw (BASHAW)
To: Frank Cross, Jr. (CROSSF)
Subject: Ciclopirox labeling

To Whom it May Concern,

Frank Cross showed me the revisions to the ciclopirox nail lacquer label that the sponsor has proposed. As to the clinical pharmacology section the sponsor is proposing three changes:

1.) Inclusion of a paragraph describing the metabolic fate of ciclopirox following other routes of administration.

2.) Adding to the (now) second paragraph wording to describe that ciclopirox was also applied to a 5mm band around each nail.

3.) Removing the words .. ———————— . from the third paragraph, where it refers to in vitro studies.

These changes are acceptable from a biopharmaceutic standpoint as they do NOT change the meaning of the section and only provide additional ·rmation in one area and clarification in two others.

Dennis Bashaw, Pharm.D.
PK Team Leader

Printed by Steve Hathaway

Electronic Mail Message

.ivity: COMPANY CONFIDENTIAL

Date: 02-Apr-1999 12:17pm
From: Steve Hathaway
HATHAWAYS
Dept: HFD-540 CRP2 N237
Tel No: 301-827-2069 FAX 301-827-2075

Subject: Tradename Consult for NDA 21-022 LOPROX Nail Lacquer

Dan,

Please see attached.

Sonya,

Please log into consults tracking log.

Tony, FYI/FYSignature

Thanks, all.

Steve

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

NC

June 25, 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

NEW CORRESP

RE: NDA 21-022
LOPROX ® (ciclopirox) Nail Lacquer 8%
Amendment: General Correspondence

Dear Dr. Wilkin:

Reference is made to the submission of the above referenced NDA to the Division on December 18, 1998. The product name in the NDA is LOPROX (ciclopirox) Nail Lacquer 8%.

On behalf of Hoechst Marion Roussel, Inc (HMRI), PAREXEL International Corporation requests the product name be changed to ———— (ciclopirox) Nail Lacquer 8%. This change is requested for the following reasons:

1. [redacted]

2. The name ———— is used outside the U.S. for ciclopirox Nail Lacquer 8%.

Expedited review is requested for this name change.

Thank you for your attention. Please contact me at (610) 565-2622, extension 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Ciclopirox Nail Lacquer 8% Launch Dates

Country	Trademarks	Launch Date
Antilla	Batrafen	00.00.94
Argentina	Loprox	01.10.92
Austria	Batrafen	00.00.96
Bolivia	Batrafen	00.00.95
Brazil	Loprox	00.03.96
Bulgaria	Batrafen	00.10.96
Chile	Batrafen	00.03.94
China	Batrafen	11.11.96
Colombia	Batrafen	00.01.97
Costa Rica	Loprox	00.09.94
Cyprus	Batrafen	00.00.96
Czech Republic	Batrafen	01.05.96
Denmark	Mycofen	00.00.93
Dominican Republic	Loprox	01.05.94
Ecuador	Batrafen	07.10.96
El Salvador	Loprox	00.09.94
France	Mycoster	02.01.92
Germany	Nagel Batrafen	15.10.92
Guatemala	Loprox	01.05.94
Honduras	Loprox	00.09.94
Hong Kong	Batrafen	02.01.97
Israel	Batrafen	11.05.95
Italy	Batrafen	00.00.96
Korea	Loprox	01.07.94
Mexico	Loprox	00.06.97
New Zealand	Batrafen	01.11.95
Nicaragua	Loprox	00.09.94
Panama	Loprox	00.09.94
Paraguay	Batrafen	02.10.95
Peru	Batrafen	26.08.94
Poland	Batrafen	00.00.96
Romania	Batrafen	00.10.96
Russia	Batrafen	00.00.95
Singapore	Batrafen	12.03.97
Slovak Republic	Batrafen	00.00.96
Spain	Ciclochem	00.05.98
Thailand	Loprox	01.12.96
Trinidad/Tobago	Batrafen	00.02.94
Turkey	Nibulen	00.05.97
Ukraine	Batrafen	00.00.97
Uruguay	Batrafen	30.05.97

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, NLRC (HFD-530)

From: Division of Dermatologic And Dental Drug Products		**HFD-540**
Attention: J. S. Hathaway, Ph.D.	**Phone :** x7-2069	
Date: July 6, 1999 (5) 7/6/99		
Subject: Request for assessment of a trademark for a proposed new drug product		
Proposed Trademark: ——— **Nail Lacquer**	**NDA 21-022**	

Established name, including dosage form:

ciclopirox topical solution - dosage form is a viscous solution, a film-forming "lacquer" similar to nail polish (no pigment)

See Consult #1174 for additional info, and the attached request.

Other trademarks by the same firm for companion products:

LOPROX Lotion (NDA 19-824)
LOPROX Cream (NDA 18-748)
LOPROX Gel (NDA 20-519)

Indications for use (may be a summary if proposed statement is lengthy):

For topical treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement due to *Trichophyton rubrum* ———

Initial comments from the submitter (concerns, observations, etc.):

The proposed tradename ——— is used on products marketed in other countries (see attached). The proposed presentation does not reflect the LNC's recommendations from Consult #1174, as this has not yet been communicated to the applicant.

Possible conflicts: ———

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1234	HFD#	540	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	J. S. Hathaway				ciclopirox topical solution
RE:	NDA/IND #	21-022			

A. Look-alike/Sound-alike

	Potential for confusion:
	___ Low ___ Medium XXX High
	___ Low XXX Medium ___ High
	___ Low XXX Medium ___ High
	XXX Low ___ Medium ___ High
	XXX Low ___ Medium ___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

___ Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date /S/ 9/10/99

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-022

SEP 13 1999

DISCIPLINE REVIEW LETTER

Hoechst Marion Roussel, Inc.
Attention: L. E. Roebel, Ph.D.
Vice-President, North American Drug Regulatory Affairs
10236 Marion Park Drive
Kansas City, MO 64137

Dear Dr. Roebel:

Please refer to your December 18, 1998 new drug application for TRADENAME (ciclopirox solution) Nail Lacquer, 8%.

We also refer to your submission dated June 25, 1999.

Our review of the chemistry section of your submissions is complete, and we have identified the following deficiencies:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact CDR Frank Cross, Project Manager, at (301) 827-2020.

Sincerely,

/S/ 9/13/99

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for the
Division of Dermatologic and Dental Drug Products,
(HFD-540)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):			FROM:	
Office of Post-Marketing Drug Risk Assessment HFD-400 (Sammie Beam)			Division of Dermatologic and Dental Drug Products HFD-540	
DATE: 11/30/99	IND NO.	NDA NO. 21-022	TYPE OF DOCUMENT: Proposed Drug Name Consult	DATE OF DOCUMENT: 11/16/99
NAME OF DRUG: Ciclopirox topical solution, 8%	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE: 12/3/99	

NAME OF FIRM: Hoechst Marion Roussel

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Proposed Tradename Consult for pending NDA. PDUFA Date 12/18/99

SIGNATURE OF REQUESTER: /S/ Frank Cross, PM 7-2063	METHOD OF DELIVERY (Check one): X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

ORIGINAL

PAREXEL

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

BL

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

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

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: December 3, 1999	DUE DATE: December 3, 1999	OPDRA CONSULT #: 99-040

TO: Johnathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

PRODUCT NAME: Penlac™
(ciclopirox)

NDA #: 21-022

MANUFACTURER: Parexel International
(For Hoescht Marion Roussel, Inc.)
Rose Ree Corporate Center
1400 N. Providence Road, Suite 2000
Media, PA 19063

CASE REPORT NUMBER(S): Not applicable.

MMARY:

In response to a consult from the Division of Dermatologic and Dental Drug Products, OPDRA conducted a review of the proposed proprietary name "Penlac™" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name Penlac™.

/S/ 12/3/99

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
x: (301) 827-5189

/S/ 12/6/99

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Hoechst Marion Roussel

December 18, 1998

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 962
Kansas City, MO 64134-0962
Telephone (816) 966-5000
U.S. Web site www.hmri.com

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

Subject: **NDA 21-022** ORIGINAL NEW DRUG APPLICATION
LOPROX ® Nail Lacquer 8%
(ciclopirox)

Dear Dr. Wilkin:

In accordance with the regulations set forth in 21 CFR 314.50, Hoechst Marion Roussel (HMRI) is submitting an original New Drug Application (NDA) for LOPROX® (ciclopirox) Nail Lacquer 8% for the topical treatment (fingernails and toenails) of mild to moderate onychomycosis without lunula involvement due to *Trichophyton rubrum*.

This NDA consists of 100 volumes, including data from two Phase III, randomized, vehicle-controlled studies in onychomycosis conducted in the United States under IND ——, involving over 400 patients. Supportive safety and effectiveness data from two Phase II studies conducted in the United States involving over 200 patients are also included.

It was agreed with the Division in a meeting which occurred August 18, 1997 that the data listings provided as appendices to the study reports would suffice and that separate patient listings need not be included in Item 11. However, subject data listings for the non-US studies are contained in Item 11.

On September 2, 1998, there was a teleconference with Frank Cross Jr., Senior Management Officer, to discuss the submission of electronic data sets to support this NDA submission. Mr. Cross requested that data sets (electronic versions of the data listings) for studies 211, 212, 312 and 313 be submitted at the time of the NDA submission. As agreed, these data sets will be sent by separate cover directly to Mr. Cross. Also being sent directly to Mr. Cross is the data set for study 111 for Biopharmaceutics reviews. Mr. Cross noted that additional data sets might be requested later.

FDA contact reports dated 9/17/96 and 9/20/96 are referenced in the study reports for the pivotal trials 312 and 313. These two contact reports, along with a copy of the FDA minutes from the August 18, 1997 pre-NDA meeting, are included in the NDA in Item 19 (Other) for ease of review.

APPEARS THIS WAY
ON ORIGINAL

Please note that on August 28, 1998 PAREXEL International Corporation received a facsimile from FDA containing comments from the Microbiology review of the June 20, 1997 meeting briefing package. We have modified the submission to address these comments.

The manufacturing facility for both the drug product and drug substance is:

Hoechst Marion Roussel Deutchland GmbH
65926 Frankfurt
Germany

Please note that the terms "Batrafen" and "Gantrez" are used in this application. These are trade names used in some European countries for ciclopirox Nail Lacquer 8%.

The user fee in the amount of ——— (User Fee ID #3497) was sent to Mellon Bank, Pittsburgh, PA on August 11, 1998.

We look forward to working with you during the review of this NDA. Please be advised the information submitted is considered confidential under 21 CFR 314.430.

HMRI hereby authorizes PAREXEL International Corporation to act on our behalf for this NDA. Communications regarding this NDA should be forwarded to:

Tracie Parker
Senior Regulatory Associate
PAREXEL International Corporation
Rose Tree Corporate Center
1400 N. Providence Road
Suite 400
Media, PA 19063
Telephone: 610-565-2622, ext. 2244
Fax: 610-565-5866

Sincerely,

L. E. Roebel, PhD
Vice President, North American Drug 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

FDA

December 21, 1998

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

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

Dear Frank:

Reference is made to the Loprox Nail Lacquer NDA submitted to the Division on Friday, December 18, 1998.

Additional reference is made to the September 2, 1998 teleconference between FDA, Hoechst Marion Roussel, Inc. and PAREXEL International during which we discussed electronic submission of data for the above referenced NDA. In accordance with agreements made during that teleconference enclosed please find diskettes containing SAS data sets for studies 111A, 211, 212, 312 and 313.

The diskettes for studies 312 and 313 include Raw Datasets and Analysis Datasets. These studies are being sent as two zipped SAS transport files created using proc copy; one file for Raw Datasets and one file for Analysis Datasets. The diskettes for studies 111A, 211 and 212 contain Raw Datasets only and will, therefore, contain one zipped SAS transport file per study.

The following files are enclosed in this submission:

CONTENTS.LIS
HMR_111A.ZIP
HMR_211.ZIP
HMR_212.ZIP

HMR_312.ZIP
HMR_312A.ZIP
HMR_313.ZIP
HMR_313A.ZIP

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

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

January 22, 1999

DRUG NEW CORRES
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%
Amendment: General Correspondence

Dear Dr. Wilkin:

Reference is made to the Loprox (ciclopirox) Nail Lacquer 8% New Drug Application submitted to the Division on December 18, 1998. Additional reference is made to an informal submission to Mr. Frank Cross on December 21, 1998 that consisted of diskettes containing SAS data sets for studies 211, 212, 312, 313 and 111A. Further reference is made to a telephone conversation of January 22, 1999 between PAREXEL and Dr. Roy Blay and Dr. Steve Thompson of the Division.

In accordance with a request made by Dr. Thompson during the above referenced telephone conversation, PAREXEL International, on behalf of Hoechst Marion Roussel, Inc., is hereby submitting, in triplicate, copies of the following:

These ——— will assist during review of the SAS data sets submitted previously. Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

PAREXEL

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

ORIGINAL NC

ORIG

February 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

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

Dear Dr. Wilkin:

Reference is made to the Loprox (ciclopirox) Nail Lacquer 8% New Drug Application submitted to the Division on December 18, 1998. Additional reference is made to a telephone conversation dated January 28, 1999 with Dr. Roy Blay, Project Manager and myself. During this conversation Dr. Blay inquired about the location of the following two statements in the NDA:

- An overall statement confirming that the controlled clinical trials in the NDA were conducted under the appropriate informed consent and IRB regulations.

  This statement is contained in each clinical study report but we are providing herein an overall statement that includes all controlled clinical studies submitted in the NDA.

- A statement confirming that the information presented in the Integrated Summary of Safety (ISS) reflects all safety information from all known sources and the cut-off date for obtaining this information..

  This statement was not included in the ISS. Enclosed herein is a statement addressing this issue.

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

NDA 21-022

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

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

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

DUPLICATE

February 11, 1999

ORIG AMENDMENT
BC 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%
Amendment: Response to Request for Additional Information

Dear Dr. Wilkin:

Reference is made to the Loprox (ciclopirox) Nail Lacquer 8% New Drug Application submitted to the Division on December 18, 1998. Additional reference is made to a facsimile from the Division dated February 5, 1999 requesting additional responses and materials needed for the review of NDA 21-022. Please see below for the Division's requests followed by our response in bolded italics.

CHEMISTRY

1. Please confirm that

Hoechst Marion Roussel Deutschland GmbH
Bruningstrasse 50
Postfach 80 03 20
D-65926 Frankfurt am Main
Federal Republic of Germany

is the sole facility proposed for manufacturing, packaging, testing and stability monitoring.

It is confirmed that all manufacturing and testing operations are carried out by Hoechst Marion Roussel Deutschland GmbH at its facility located in Frankfurt/-Main. Reference is also made to Volume 1.2, Pages 054 to 060 of the application.

Please confirm that you have provided the following information requested by citing volume and page references for each item and sub-item:

2. The final rule on Environmental Assessments was published on July 29, 1997, and has an effective date of August 28, 1997. This rule should be closely examined to assess if a categorical exclusion can be requested.

   It is confirmed that a categorical exclusion is requested in accordance with the final rule on Environmental Assessments published in the Federal Register as of July 29, 1997, Volume 62, Number 145. Reference is also made to Volume 1.2, Page 354 of the application.

3. The sponsor should be advised that it would be more appropriate to cross reference all drug substance information from the approved NDA 18-748.

   NDA 18-748 for Loprox Cream 1% refers to ciclopirox olamine as drug substance whereas NDA 20-519 for Loprox Gel 0.77% refers to the free acid ciclopirox. Since ciclopirox (free acid) is the active ingredient of Loprox Nail Lacquer 80 mg/g, it seems to be more appropriate to cross-reference the NDA 20-519.

Additional Guidance for the NDA submission:

4. Please provide a statement of readiness for inspections. All facilities connected with the proposed NDA should be listed with their CFN #s, contact person and phone number.

   The Frankfurt site is ready for the inspection. The site registration number (CFN number) for the Frankfurt/Main site is ——— The following persons from the site can be contacted:

APPEARS THIS WAY
ON ORIGINAL

KEL

Name	*Department*	*Phone Number*
Dr. Barbara Bassler	***Quality Operations/Quality Assurance Drug Products***	***49-69-305-83186***
Dr. Gerd Fischer	***Quality Operations/Quality Assurance Drug Substances***	***49-69-305-17932***

5. Please provide at least one copy of an unexecuted batch record of a lot utilized in the clinical studies and the latest revision of a batch record which will be used in commercial manufacturing. A brief description of the production and packaging process for a typical batch (including type of equipment, operating conditions, sampling points). A schematic diagram may be useful. The manufacture of the key clinical batches and production batches must be compared if they differ.

A copy of the English translation of an unexecuted batch manufacturing record used for a clinical batch is enclosed as Attachment 1. Regarding the currently valid master batch record for this product, reference is made to Volume 1.2, Pages 067 to 082 of the application. An English translation is provided on Pages 084 to 099 of Volume 1.2. For a brief description of the production and packaging process reference is made to Volume 1.2, Pages 064 and 127. The sampling points are included in the flow chart on Page 063 of the same volume. The manufacturing processes used to produce the clinical batch and the current commercial batches are essentially the same. The batch size was doubled from [redacted] This was taken into account by [redacted]

6. Provide a list of all the in-process controls (and limits) used during the various stages of the manufacturing operations; include a short description and the frequency of testing if the particular control needs explanation.

The in-process controls and acceptance criteria used during the various stages of the manufacturing operations are listed in Volume 1.2, Page 065 of the application. In addition to these in-process controls the following tests are carried out as mentioned in the master batch manufacturing record in Volume 1.2, Pages 067 to 082 of the application:

APPEARS THIS WAY
ON ORIGINAL

EL

Test Item	*Manufacturing Step**	*Acceptance Criteria*

- *according to the flow chart in Volume 1.2, Page 063*

All tests are carried out routinely for each batch of the product using standard procedures as laid down in the USP.

7. Please describe the role of each of the excipients in the final formulation.

Reference is made to Volume 1.2, Page 002, detailing the components and their function. Reference is also made to Volume 1.1, Page 181, Paragraph 2.2.

8.

9. The drug product specifications and limits should be updated in accordance with the latest guidance. Please be advised that the proposed assay method is not stability indicating and a stability indicating assay should be provided in the NDA.

The specifications of the drug product cover tests on identification, chemical/-microbiological purity and the content of the active ingredient as required by the appropriate ICH guideline. Reference is made to Volume 1.2, Page 132 of the application. The chemical purity and the content are assessed by a ——— method allowing the detection and quantitation of degradation products. Reference is made to Volume 1.2, Pages 146 to 166 of the application.

10. A summary of the sampling plan for the components of the container/closure system should be provided.

A representative number of samples is withdrawn by the suppliers throughout the production process of the container / closure system. The number of samples required is laid down by Hoechst Marion Roussel (HMR) depending on the size of the batch, the physical and chemical tests to be carried out, and the number of retention samples to be stored by HMR. The samples are sent to HMR together with the delivery of each batch.

11. A summary of the container/closure system compatibility with the drug product should be provided.

The compatibility of the product with the container/closure system is proved by stability test results obtained after storage for up to — months under normal and up to — months under accelerated conditions. Reference is made to Volume 1.2, Pages 217 to 241 of the application. Moreover, the drug product has been approved and is marketed in 38 countries around the world since several years.

12. Please be advised that a statement of the proposed expiration dating period, and the stability commitment and protocol should be included, as well as information about post-marketing stability plans (e.g., compliance with CGMP stability testing and reporting requirements).

An expiration dating period of — months is proposed for Loprox Nail Lacquer. Reference is made to the stability report in Volume 1.2, Pages 219 to 241 of the application. This report details the test materials, storage conditions and analytical test results obtained from the study and the conclusions with regard to the expiration dating period and storage directions. A post-approval testing commitment is provided in Volume 1.2, Page 301 of the application. Furthermore, the stability protocol for the post-approval stability studies is included in Volume 1.2 on Pages 302 to 306.

It should be noted that for each of the stability protocol(s) the following information should be included:

13. General product information [e.g., strength, size of container; etc.]

Detailed information on the test material, composition, packaging, storage conditions and analytical procedures is given in the stability protocol for post-approval stability studies in Volume 1.2 on Pages 304, 305 and 306.

14. Stability study design; i.e., a brief summary of specs/tests, method, sampling plan. duration. A created table may be appropriate.

Please refer to our response to #13 above.

15. Stability data; lot number, date of manufacture.

The storage conditions are defined in the post-approval stability protocol in Volume 1.2, Page 305 of the application. The batch number and date of manufacture of the batches to be tested are not part of the protocol since these data are not available until the study begins. These data will be submitted to the agency in annual progress reports.

STATISTICS

———————: the SAS data sets (including annotated case report forms).

In accordance with a request made by Dr. Steve Thompson during a telephone conversation dated January 22, 1999, ——————— studies 211, 212, 312, 313 and 111A were submitted as an amendment to the NDA. The submission was dated January 22, 1999.

BIOPHARMACEUTICS

The Human Pharmacokinetics and Biopharmaceutics section (including tables and figures) on disk in Word 97.

As per a conversation with Dr. Roy Blay on February 9, 1999, the biopharmaceutics reviewer is requesting the summary only from this section on disk at this time. Enclosed as Attachment 2 please find a diskette containing this summary. This disk is labeled as "HPK/BA Summary from Loprox Nail Lacquer NDA 21-022".

MICROBIOLOGY

Desk copies of volumes 3, 4, 5, 14, 24, 34, 43, 57 and 62.

Desk copies of the volumes listed above are enclosed herein.

CLINICAL

The clinical protocols on disk in Word 97.

Please refer to Attachment 3 for a diskette labeled "Protocols for Studies 312 and 313 from Loprox Nail Lacquer NDA 21-022" for the protocols for the "pivotal" studies, studies 312 and 313. Please note that we do not have these protocols available electronically so we scanned them into Word. Therefore, some graphs and tables did not come through properly. You will need to refer to the hard copy of the protocol for reference to any tables or graphs.

This scanning task is in progress for the other clinical protocols. We expect to have the rest of the protocols available electronically to submit to the Division during the week of February 15, 1999.

MISCELLANEOUS

Six desk copies of Volume 1.1

These copies are enclosed herein.

PAREXEL International, on behalf of Hoechst Marion Roussel, Inc., hereby amends NDA 21-022 with the information contained in this submission.

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

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

ORIGINAL

BM NC

ORIG AMENDMENT

February 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)
9201 Corporate Boulevard
Building 2; 2nd Floor; Room N214
Rockville, MD 20850

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

Dear Dr. Wilkin:

Reference is made to the Loprox (ciclopirox) Nail Lacquer 8% New Drug Application submitted to the Division on December 18, 1998. Additional reference is made to a facsimile from the Division dated February 5, 1999 requesting additional responses and materials needed for the review of NDA 21-022. Further reference is made to our February 11, 1999 response to your request. In that response we included diskettes containing electronic versions of protocols for studies 312 and 313 and we stated that we would submit the rest of the protocols submitted in this NDA at a later time.

Accordingly, please find enclosed diskettes containing protocols for the remaining studies (111A, 211, 212, 320 and 1003) that were submitted in NDA 21-022. Please note that we do not have these protocols available electronically so we scanned them into Word. Therefore, some graphs and tables did not come through properly. You will need to refer to the hard copy of the protocol for reference to any tables or graphs.

PAREXEL International, on behalf of Hoechst Marion Roussel, Inc., hereby amends NDA 21-022 with the information contained in this submission.

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

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

March 8, 1999

NDA ORIG AMENDMENT
BM
NC

Jonathan Wilkin, MD
Director
CDER
U.S. Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD-540)
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

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

Dear Dr. Wilkin:

Reference is made to Dr. Roy Blay's voice mail message dated February 17, 1999 requesting that we query the WHO database for adverse experiences related to any of the ciclopirox-containing compounds. PAREXEL International Corporation, on behalf of Hoechst Marion Roussel, Inc., hereby amends NDA 21-022 with the requested information.

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

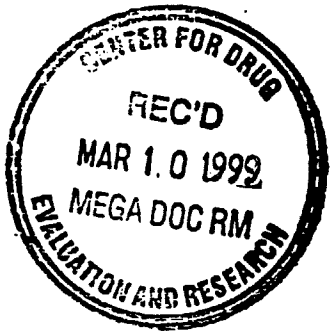
Tracie A. Parker
Manager, Regulatory Operations

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

ORIGINAL



March 9, 1999 **NDA ORIG AMENDMENT**

BMNC

Jonathan Wilkin, MD
Director
CDER
U.S. Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD-540)
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

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

Dear Dr. Wilkin:

Reference is made to Dr. Roy Blay's facsimile dated February 23, 1999 requesting responses to the following clinical comments:

1. An estimate of maximum grams of human exposure per application of ciclopirox nail lacquer, 8% to all fingernails and all toenails is requested. In addition to the nail plate, the estimate should include application onto 5 mm of the proximal and lateral nail fold areas, ventral surface of the nail plate if free of the nail bed, etc. as instructed per protocol (Vol. 34, pg. 028).

2. Please provide the volume of liquid applied per application and the weight in grams per ml of liquid applied to all fingernails and toenails.

Please see Attachment 1 of this submission for our response to the above comments. Additionally, Attachment 2 of this submission contains a copy of a study report (HOE296NL/3/D/1002) entitled, "Study to Determine the Amount of Ciclopirox 8% Nail Varnish Required per Application in Comparison to a Comparable Customary In-Trade Product" that supports our response.

PAREXEL International Corporation, on behalf of Hoechst Marion Roussel, Inc., hereby amends NDA 21-022 with the requested information as enclosed. Thank you for your attention.

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Worldwide Regulatory Operations

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

PAREXEL

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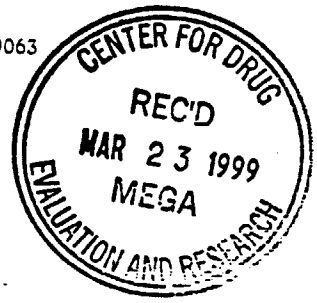


NEW CORRESP
NC

March 22, 1999

Jonathan Wilkin, MD
Director
CDER
U.S. Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD-540)
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

RE: NDA 21-022
Loprox® (ciclopirox) Nail Lacquer 8%
Submission of DESK COPY

Dear Dr. Wilkin:

Reference is made to our February 11, 1999 amendment to the Loprox Nail Lacquer 8% NDA (NDA 21-022) consisting of our Response to the Division's Request for Additional Information. One of the items contained in this response was a diskette containing an electronic version of the Human Pharmacokinetic and Bioavailability Summary from the NDA. Enclosed herein, on behalf of Hoechst Marion Roussel, Inc., please find a Desk Copy of this diskette in accordance with Dr. Roy Blay's request dated March 19, 1999.

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

PAREXEL

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

Attachment 1

Attachment 2

6M

April 21, 1999

NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Director
CDER
U.S. Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD-540)
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

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, 1999. Further reference is made to a telephone message from Dr. Roy Blay on April 5, 1999. During this message Dr. Blay requested the following information be submitted to the NDA:

1. For Study 111A – Individual demographic data including weight for each individual and disease conditions including the severity and area of involvement for each of the fingernails and toenails and the individual daily dose

   ATTACHMENT 1 provides volume and page number locations of the above information in the original NDA.

2. For Studies 312 and 313 – The numbers of toenails and fingernails treated for each patient who participated in the PK sampling who were on active treatment and the individual daily dose.

   ATTACHMENT 2 consists of two tables containing this information (one table for study 312 and one table for study 313).

ORIGINAL

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Regulatory Operations

BM
NDA ORIG AMENDMENT

APPEARS THIS WAY
ON ORIGINAL

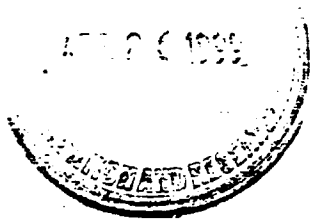
ORIGINAL

Attachment 1

Attachment 2

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

April 23, 1999

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

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. Further reference is made to a facsimile from Dr. Roy Blay dated April 6, 1999 which listed information requested by Dr. Vaughan. This submission contains our response to the four requests listed below:

1. *SAS data sets for the following normal and abnormal laboratory parameters on a per lab visit per patient treatment basis in a tabular summary. Please include patient ID, trial center, age, sex, and concomitant ciclopirox medication stratified by treatment for:*

   a) *serum creatinine phosphokinase levels*
   b) *serum creatinine phosphokinase-MB levels*

   Attachment 1 contains tabular listings of this information as well as a diskette containing the SAS data sets.

2. *On disk in Word Format:*

   a) *integrated summaries of efficacy and safety*

b) study synopses for studies 211, 212, 312, 313 and 320

Attachment 2 consists of a diskette containing Word versions of the ISE and ISS and one diskette containing Word versions of the study synopsis from studies 312 and 313. We are in the process of scanning the hard copies of the study synopses from studies 211, 212 and 320 and will submit the electronic copies from these study reports under separate cover.

3. *Case Report Form for patient 053/0412 (from Study 320 and 312).*

Attachment 3 contains a copy of the case report form (CRF) for Patient 0412 from study 312 and a copy of the CRF for the same patient from study 320. Please note, your request indicates investigator 053 but the investigator for patient 0412 is actually 052.

4. *Additional data requested for #870781537 from WHO database (submission dated 03/08-99).*

See Attachment 4 for this information.

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

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Worldwide Regulatory Operations

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

NEW CORRESP

PAREXEL

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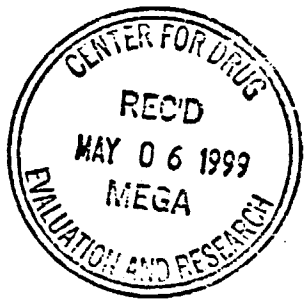
Fax: (610) 565-5223



May 5, 1999

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

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 a facsimile from Dr. Roy Blay dated April 6, 1999 that listed information to be submitted requested by Dr. Vaughan. Further reference is made to our response to Dr. Blay's April 6, 1999 facsimile dated April 23, 1999.

In our April 23, 1999 response, we indicated that electronic versions of the synopses from studies 211, 212 and 320 would be submitted under separate cover. Enclosed please find a diskette, submitted in duplicate, containing Word versions of these study synopses to complete our response to FDA's Request for Information dated April 6, 1999.

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

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Worldwide Regulatory Operations

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

RECD
MAY 06 1999

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	May 5, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
(816) 966-5000	(816) 966-6790

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
10236 Marion Park Drive
Kansas City, MO 64137-1405

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
PAREXEL International Corporation
195 West Street
Waltham, MA 02154
(781) 466-8833

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-022

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ciclopirox nail lacquer 8%	LOPROX

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*: HOE 296

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
nail lacquer	8%	topical

(PROPOSED) INDICATION(S) FOR USE
for the topical treatment of mild to moderate onychomycosis without lunula involvement due to Trichophyton rubrum. It is indicated for the treatment of fingernails and toenails.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to FDA Request for Information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attached

PAREXEL

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

ORIGINAL

BP -

AMENDMENT

May 18, 1999

Jonathan Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 21-022
Loprox®(Ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information

Dear Dr. Wilkin:

As requested by Mr. Frank Cross during a telephone conversation dated May 17, 1999, enclosed please find two copies of an amendment made to our _____ on April 19, 1999 (Serial Number 014). PAREXEL International are amending NDA 21-022 with the enclosed information on behalf of Hoechst Marion Roussel, Inc.

Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,

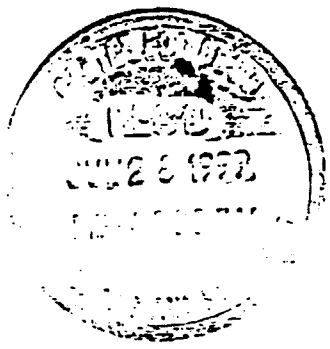
Tracie A. Parker
Manager, Worldwide Regulatory Operations

ORIGINAL
NC

PAREXEL

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

ORIG AMENDMENT



July 27, 1999

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Bldg 2, 2nd floor
Room N229
Rockville, MD 20850

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. Further reference is made to our submission to the Division dated April 21, 1999 in response to FDA's request for information. Additional reference is made to Mr. Frank Cross' telephone conversation with Ms. Alicia Cabrelli, Regulatory Associate at PAREXEL International, dated July 21, 1999 during which Mr. Cross requested that we submit a diskette containing the data listings, in Word format, included in our April 21, 1999 submission.

Included in this submission please find a diskette containing the following data listings (the parentheses "[]" contain the name of the file on the enclosed diskette in bold):

From Study 111A:

Listing I.2 – Demographics **[i_2]**
Listing I.8 – Daily Dosage **[i_8]**
Listing I.9 – Drug Accountability **[i_9]**
Listing II.9 – Vital Signs **[ii_9]**
Listing IV.2 – Clinical Evaluation **[iv_2]**
Listing IV.3 – Investigator's Evaluation **[iv_3]**

From Studies 312 and 313:

Listing of Number of Fingernails and Toenails Treated with Dosage Information for Subjects Who Participated in the PK Sampling **[pkpts]**

Also included on the enclosed diskette, for additional information, are data listings relating to the serum creatinine phosphokinase levels that were submitted to the Division on April 23, 1999. This file is called **cpklab**.

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. 2244 if you have any questions.

Sincerely,

Tracie A. Parker
Manager, Worldwide Regulatory Operations

APPEARS THIS WAY
ON ORIGINAL

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

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ATTACHMENT 1

August 5, 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 the teleconference with Mr. Frank Cross and Dr. Susan Walker of the Division and Ms. Tracie Parker of PAREXEL. Further reference is made to the facsimile from FDA dated August 4, 1999.

During the above referenced teleconference, Dr. Walker requested the following information:

1. Case Report Form for Patient 1802 in Study 313.
   See ATTACHMENT 1.

2. Blank Case Report Form for Study 313.
   See ATTACHMENT 2. (A blank case report form for study 313 is located in the NDA in Volume 1.44; page 134).

3. Explanation of the discrepancies in designation of target great toenail noted in Study 313, volume 1.46, Data Listing 5.2.

   Data Listing 5.2 for studies 312 and 313 contained a programming error. These two data listings have been rerun and are contained in ATTACHMENT 3. There are no programming errors contained in any of the other tables or in Listing 4 for these studies.

Please note that this submission also addresses issue #7 on the facsimile dated August 4, 1999 from Mr. Cross to Ms. Parker. A separate submission will follow addressing issues numbered 1-6 on this facsimile.

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

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NEW CORRESP

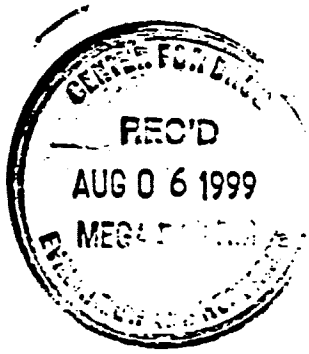
Hoechst Marion Roussel

August 5, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Jonathan Wilkin, MD
Director
Center for Drug Evaluation and Research
Division of Dermatologic Drug Products
(HFD-540)
Food and Drug Administration
9201 Corporate Blvd, Bldg. 2, 2nd floor
Room N229
Rockville, MD 20850



Re: _____
(ciclopirox)

Dr. Wilkin:

Hoechst Marion Roussel, Inc., hereby authorizes the Food & Drug Administration to cross-reference the following applications during the review of this NDA.

Approved NDAs:

LOPROX® (ciclopirox) Cream 0.77% (Formerly LOPROX® (ciclopirox) Cream 1%)	NDA 18-748
LOPROX® (ciclopirox) Lotion 0.77% (Formerly LOPROX® (ciclopirox) Lotion 1%)	NDA 19-824
LOPROX® (ciclopirox) Gel 0.77%	NDA 20-519

Pending NDA:

LOPROX® (ciclopirox) Nail Lacquer 8%	NDA 21-022

Open IND:

_____ _____

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PAREXEL

Reservoir Place, 1601 Trapelo Rd., Waltham, MA 02154
Telephone: (781) 466-8833
Fax: (781) 466-6394

ORIG AMENDMENT

August 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
LOPROX® (ciclopirox) Nail Lacquer 8%
Response to FDA Request for Information dated August 4, 1999

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 4, 1999.

PAREXEL International Corporation hereby amends NDA 21-022 with the above requested information on behalf of Hoechst Marion Roussel, Inc. Please note that "ATTACHMENT" refers to materials contained in the present submission.

The following information was requested in the facsimile:

1. ***Location in the NDA submission of a description of the "computerized photoplanimetric method" used to determine percent involvement for Studies 312 and 313.***

   Photographic Procedures for studies 312 and 313 are included as an appendix to each protocol. This information is contained in the NDA Volume 1.35, pg. 054-055 for study 312 and Volume 1.44, pg. 122-123 for study 313. These are also included as hard copy in ATTACHMENT 1-1. We are also enclosing a copy of the SOP that provides the procedures for planimetric measurements from the photographic monitor for studies 312 and 313. Please refer to ATTACHMENT 1-2.

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.***

   The location of Treatment Emergent Adverse Events Table (Table III.1A) is located in Volume 1.60, pg. 059 of the NDA. A diskette containing this table in Word format is provided in ATTACHMENT 2-1. For your convenience, ATTACHMENT 2-2 also includes a hard copy.