CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-022

ADMINISTRATIVE DOCUMENTS

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 3, 1999

NDA NUMBER: 21-022

NAME OF DRUG: Penlac™ Nail Lacquer (ciclopirox topical solution 8%)

NDA HOLDER: Parexel International, Rose Ree Corporate Center, 1400 N. Providence Rd, Suite 2000, Media, PA 19063 (Submitted on behalf of Hoescht Marion Roussel, Inc.)

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for assessment of an alternate proprietary name proposed by the sponsor. ——— was the proprietary name initially submitted to the Labeling and Nomenclature Committee (LNC), with a response provided by the LNC on August 31, 1999. ——— was found to be unacceptable by the LNC.

"Penlac™ Nail Lacquer (ciclopirox) Topical Solution, 8%", the name as proposed by the sponsor, is a product indicated for the treatment of nail fungal infections. Three other ciclopirox products are currently marketed in the U.S., all with the proprietary name Loprox™ (ciclopirox topical gel 0.77%, ciclopirox olamine topical cream 1%, and ciclopirox olamine topical lotion 1%). The current NDA holder for all three products is Hoescht Marion Roussel, Inc. (HMRI).

II. SAFETY AND RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases (the Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book) for existing drug names which sound alike or look alike to Penlac™ to a degree where potential

confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[iv]. A focus group discussion was conducted to review all findings from the searches.

Two product names were reviewed in the focus group which were thought to have minimal potential for confusion. Rondec™, a currently marketed product, and ——— a product for which the IND and NDA have been withdrawn, were discussed as proprietary names for which look-alike medication errors might occur. Also, potential verbal confusion with the proprietary names Prozac™ and Teslac™ was discussed. *Although there was insufficient time for a full survey and analysis to be performed upon this occasion, it was thought that confusion of Penlac™ with any of these drug product names was unlikely, given the differences in dosage forms, available strengths, and usual dosing regimens of these products.*

Safety concerns were raised, however, regarding the approval of a different proprietary name for a product with the same active ingredient as other related products of the same manufacturer (HMRI). The creation of a new name for a product with the same active ingredient and same manufacturer adds unnecessarily to the growing number of proprietary names in the U.S. *For this reason, approval of the name Penlac™ was not recommended.*

We recommend continued use of the trade name Loprox™ for this addition to the line of HMRI products. This has been discussed with the Division (HFD-540). However, with consideration of the facts that ——— the following practical solutions are suggested. HMRI has also made some assertion at a previous date that this product, ciclopirox topical solution 8%, ——— Assuming approval of this product, a trade name does not need to be submitted by the manufacturer at the time of its approval. A labeling supplement can be filed at a later date to request approval of the proprietary name chosen. An alternate suggestion is approval of the trade name Penlac™, with a signed agreement from Parexel/HMRI that the trade name Penlac™ will not be used in the U.S., particularly while HMRI is the NDA holder for the existing ciclopirox products.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

The proposed package insert and product labeling (e.g., carton and container labels) were not available at the time of this review.

IV. RECOMMENDATIONS

OPDRA does not recommend use of the proprietary name Penlac™. The firm should be requested to seek approval of this NDA without a proprietary name and to file a supplement for Loprox™ ———

OPDRA would appreciate feedback on the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/ 12/3/99

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-022
HFD-540; Division Files/Frank Cross, Project Manager
HFD-540; Jonathan Wilkin, Division Director
HFD-540; Claudia Karwoski, Safety Evaluator, DDREI, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

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[i] MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).
[ii] American Drug Index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
[iii] Facts and Comparisons, Updated October 1999, Facts and Comparisons, St. Louis, MO.
[iv] WWW location http://www.uspto.gov/tmdb/index.html.

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1174	HFD#	540	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Steve Hathaway			Loprox Nail Lacquer	ciclopirox

A. Look-alike/Sound-alike

Potential for confusion:

	Low		Medium		High
	Low		Medium		High
	Low		Medium		High
	Low		Medium		High
	Low		Medium		High

B. Misleading Aspects:

C. Other Concerns:

The recommended presentation is:

LOPROX Nail Lacquer
(ciclopirox topical solution)

D. Established Name

____ Satisfactory
xxx Unsatisfactory/Reason

Recommended Established Name
ciclopirox topical solution

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 6/7/99

APPEARS THIS WAY
ON ORIGINAL

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. Steve Hathaway	**Phone :** 301-827-2069
Date: April 2, 1999		
Subject:	Request for assessment of a trademark for a proposed new drug product	
Proposed Trademark:	LOPROX® (ciclopirox) Nail Lacquer	**NDA 21-022**

Established name, including dosage form:

LOPROX® (ciclopirox) Nail Lacquer, 8%

Other trademarks by the same firm for companion products:

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

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

"... for topical treatment of mild to moderate onychomycosis without lunula involvement due to *Trichophyton rubrum* ——— It is indicated for the treatment of fingernails and toeails."

APPEARS THIS WAY
ON ORIGINAL

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

The established name incorporates the recent change in the USP from "ciclopirox olamine" to "ciclopirox".

Early discussions between reviewer and Labeling Standards Technical Committee suggest a possible problem with the dosage form "Nail Lacquer", which apparently is not an accepted dosage form. While the drug product seems to be a homogeneous solution in staorage, the persistent nature of the drug as applied (the hard coating formed after drying) is sufficiently unique to warrant further discussion toward adoption of this term as an acceptable dosage form.

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

EXCLUSIVITY SUMMARY FOR NDA # 21-022 SUPPL.#_____

Trade Name TRADENAME® NAIL LACQUER, 8%
Generic Name ciclopirox topical solution, 8%

Applicant Name Hoechst Marion Roussel HFD # 540

Approval Date If Known 12/17/99

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-519, Loprox Gel, 0.77%
NDA# 18-748, Loprox Cream, 1%
NDA# 19-824, Loprox Lotion, 1%

Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

HOE 296NL/8/USA/312/NM
HOE 296NL/8/USA/313/NM

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #[redacted] YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND [redacted] YES /_X__/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /_X__/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /_X__/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X/

/S/ 11/30/99

Signature Date

Title: Project Manager

/S/ 12/8/99

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PHASE 4 COMMITMENT FROM November 26, 1999, MO REVIEW

The safety database for application of this product to the fingernails is incomplete. Phototoxicity and photocontact allergenicity studies were not submitted to the NDA in support of safety. Absorption maximum at 302 plus/minus 2 nm is reported for ciclopirox (Vol. 1.1, pg. 189). As there is absorption in the UV range for the drug substance, phototoxicity and photoallergenicity studies are required

Given the minimal signal in the finger-nail trials, the Sponsor has some, but indegrate, evidence of safety. A Phase 4 commitment is sufficient to complete the needed information. /S/ 12/8/99

APPEARS THIS WAY
ON ORIGINAL

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

Elaine Waller

Elaine Waller, Pharm D
Vice President,
North American Drug Regulatory Affairs

20 May 98
Date

APPEARS THIS WAY
ON ORIGINAL

ITEM 13. PATENT INFORMATION

US Patent Number	Expiration Date	Type of Patent	Patent Owner
4,957,730	September 17, 2007	Drug Drug Product Method of Use	Hoechst AG

ITEM 14. PATENT CERTIFICATION

Declaration under 21 CFR 314.53(c)(2)

The applicant declares that Patent No. US 4,957,730 covers the drug ciclopirox, the drug product ciclopirox nail lacquer 8% (antimycotic nail varnish) and its method of use.

This product is subject of this application for which approval is sought.

Declaration under 21 CFR 314.108

The applicant claims exclusivity of three years from the date of approval as provided by the Drug Price Competition and Patent Term Restoration Act of 1984.

ADVISORY COMMITTEE

Dermatologic and Ophthalmic Drugs Addvisory Committe conducted on November 4, 1999. Transcripts and minutes are available from the Advisors and Consultants Staff.

FORM FDA 356h

NDA 21-022

ESTABLISHMENT INFORMATION

The drug substance is manufactured and supplied by:

Hoechst Marion Roussel Deutschland GmbH
Bruningstrabe 50
D-65926 Frankfurt au Main
Federal Republic of Germany

The drug product is manufactured, packaged and labelled by:

Hoechst Marion Roussel Deutschland GmbH
Bruningstrabe 50
D-65926 Frankfurt au Main
Federal Republic of Germany

Cross References:

IND [redacted]	Loprox (ciclopirox) Nail Lacquer 8%
NDA 18-748:	Loprox (ciclopirox olamine) Cream 1%
NDA 19-824:	Loprox (ciclopirox olamine) Lotion 1%
NDA 20-519:	Loprox (ciclopirox) Gel 0.77%

APPEARS THIS WAY
ON ORIGINAL