

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-159

**CHEMISTRY REVIEW(S)**

**NDA 21-159**

**Loprox (ciclopirox) Shampoo, 1%**

**Medicis Pharmaceutical Corporation**

**Mamta Gautam-Basak, Ph.D.**  
**Division of Dermatologic and Dental Drug Products**

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**APPEARS THIS WAY  
ON ORIGINAL**

# Chemistry Review Data Sheet

1. NDA 21-159
2. REVIEW #3
3. REVIEW DATE: February 21, 2003
4. Mamta Gautam-Basak, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Chemistry Review #1	2000-08-24
Chemistry Review #2	2000-06-21

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 21-159/BZ	2002-09-03
NDA 21-159/BC	2002-09-20
NDA 21-159/BZ	2003-02-10
NDA 21-159/BL	2003-02-19

7. NAME & ADDRESS OF APPLICANT:

Name: Medicis Pharmaceutical Corporations  
The Dermatology Company  
Address: 8125 North Hayden Road  
Scottsdale, AZ 85258  
Representative: Mitchell S. Wortzman, Ph.D.  
Telephone: (602) 808-0822

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Loprox
- b) Non-Proprietary Name (USAN): Ciclopirox
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

### 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Shampoo

12. STRENGTH/POTENCY: 1% (w/w)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

SPOTS product – Form Completed

Not a SPOTS product

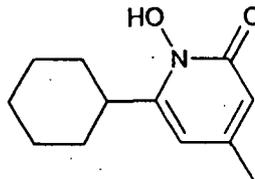
### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

6-Cyclohexyl-1-hydroxy-4-methyl-2-(1H)pyridinone

Molecular Formula:  $C_{12}H_{17}NO_2$

Molecular Weight: \_\_\_\_\_

CAS No.: 123-99-9



**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
/	III		—	4	Adequate		Information reviewed in the NDA
	III		—	4	Adequate		Information reviewed in the NDA
	III		—	4	Adequate		Information reviewed in the NDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION No.	DESCRIPTION
IND	—	
NDA	18-748	Loprox Cream, 0.77%
NDA	19-824	Loprox Gel, 0.77%
NDA	20-519	Loprox Gel, 0.77%
NDA	21-022	Penlac Nail Lacquer Topical Solution, 8.0%

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	02-12-2003	Mamta Gautam-Basak, Ph.D.
Pharm/Tox	DP impurities - Acceptable	02-04-2003	Barbara Hill, Ph.D.
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending	02-21-2003	Mamta Gautam-Basak, Ph.D.
OPDRA	Trademark acceptable		
EA	CE, acceptable	08-24-2000	Mamta Gautam-Basak, Ph.D.
Microbiology	N/A	02-21-2003	Mamta Gautam-Basak, Ph.D.

APPEARS THIS WAY  
ON ORIGINAL

# The Chemistry Review for NDA 21-159

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls (CMC) standpoint, an approval (AP) action is recommended.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

The drug substance, ciclopirox is a broad-spectrum antifungal agent with some antibacterial activity. Ciclopirox is the unsolvated form of ciclopirox olamine, which is controlled by a USP monograph and is currently approved for use in the US in a number of topical formulations (NDAs 18-748, 19-824, 20-519). Detailed CMC information pertaining to chemistry, manufacturing and controls of the drug substance is provided by reference in the approved NDA 20-519.

The proposed drug product, Loprox Shampoo, is a colorless translucent solution for topical application containing ciclopirox in a concentration of 1% in an aqueous matrix containing anionic surfactants (sodium laureth sulfate and disodium laureth sulfosuccinate) and thickening agents (laureth-2 and sodium chloride). The production processes and controls described for the commercial product are the same as those used for production of primary stability batches. The specification for the drug product is based on the recommendations in ICH Q6A document.

The proposed primary container for the to-be-marketed product is described as a low-density polyethylene (LDPE) white bottle with a white polypropylene (PP) screw cap. The filled bottles are packaged as 30-mL (physician sample) and 120-mL (to-be-marketed product).

#### B. Description of How the Drug Product is Intended to be Used

**Executive Summary Section**

Loprox Shampoo, 1% is indicated for topical treatment of seborrheic dermatitis of the scalp in adults. One to two (2) teaspoons of Loprox Shampoo are applied twice per week to the scalp and washed off after 3 minutes. The duration of use of is indicated to be 4 weeks.

A thirty-six (36) month expiration-dating period is supported based on real time data for 3 development batches, as well as three additional primary stability batches. Regression analysis results of the stability data at 95% confidence limits supports the proposed expiry.

**C. Basis for Approvability or Not-Approval Recommendation**

The composition and manufacturing process for clinical trial batches is similar to the to-be-marketed formulation. The batches used in *pivotal* studies are manufactured using the same controls as proposed for the to-be-marketed product. Analytical results (including stability data) for the to-be-marketed white LDPE bottle/white PP cap configuration is adequate to assure the quality of the product through its expiry.

An overall recommendation regarding the cGMP compliance of all manufacturing and testing facilities is acceptable per EER dated February 12, 2003.

**III. Administrative****A. Reviewer's Signature**

Chemist:  
Mamta Gautam-Basak, Ph.D.

**B. Endorsement Block**

Chemistry Team Leader:  
Wilson H. DeCamp, Ph.D.

**C. CC Block**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Mamta Gautam-Basak  
2/26/03 08:25:20 AM  
CHEMIST

Wilson H. DeCamp  
2/26/03 09:42:34 AM  
CHEMIST  
concur with review

**APPEARS THIS WAY  
ON ORIGINAL**

**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*13 pages*

AUG 24 2000

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

HFD-540

Review of Chemistry, Manufacturing, and Controls

**NDA #:** 21-159      **CHEM.REVIEW #:** 1      **REVIEW DATE:**      22-AUG-2000

<b><u>SUBMISSION/TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
ORIGINAL	30-AUG-1999	01-SEP-1999	21-SEP-1999
AR	08-SEP-1999	08-SEP-1999	21-SEP-1999
BC	17-APR-2000	18-APR-2000	21-APR-2000
BC	06-JUN-2000	15-JUN-2000	22-JUN-2000
BC	09-JUN-2000	12-JUN-2000	15-JUN-2000
BC	13-JUL-2000	21-JUL-2000	25-JUL-2000
BC	17-JUL-2000	25-JUL-2000	31-JUL-2000
BL	20-JUL-2000	24-JUL-2000	31-JUL-2000
BC	25-JUL-2000	26-JUL-2000	31-JUL-2000
BC	10-AUG-2000	11-AUG-2000	16-AUG-2000

**NAME & ADDRESS OF APPLICANT:**

Medicis Pharmaceutical Corporation  
8125 North Hayden Road  
Scottsdale, AZ 85016  
Tel: (602) 808-0822

Lynn C. Hansen  
Regulatory Affairs Manager

**DRUG PRODUCT NAME**

Proprietary:  
Nonproprietary/USAN:  
Code Names/#'s:  
Chemical Type:  
Therapeutic Class:

Loprox Shampoo 1%  
Ciclopirox  
NA  
Pyridinone  
3S

**ANDA Suitability Petition/DESI/Patent Status:**      N/A

**PHARMACOLOGICAL  
CATEGORY/INDICATION:**

For the treatment of seborrheic dermatitis of  
the scalp and:

**DOSAGE FORM:**  
**STRENGTHS:**  
**ROUTE OF ADMINISTRATION:**  
**DISPENSED:**

Shampoo  
1.0%  
Topical  
 Rx     OTC

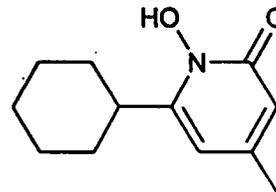
**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:**

6-Cyclohexyl-1-hydroxy-4-methyl-2-(1H)pyridinone

Molecular Formula:      C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>

Molecular Weight:

CAS Number:      [29342-05-0]



**SUPPORTING DOCUMENTS:**

No. / Type	Subject	Holder	Status	Review Date	Letter Date
			Current	N/A	11/23/99
			Current	8/22/00	3/21/2000
NDA 18-748	LOPROX Cream, 0.77%		Current		N/A
NDA 20-519	LOPROX Gel, 0.77%		Current		N/A
NDA 21-022	Penlac Nail Lacquer Topical solution, 8%		Current		N/A
			Current		N/A

**CONSULTS:** Microbiology (see Attachment #3)

**REMARKS/COMMENTS:**

During review of this NDA, USP 24/NF 19 was published, effective January 1, 2000. Revision of the established name of the drug substance from "ciclopirox olamine" to "ciclopirox", per earlier recommendation by FDA CMC reviewers, has not yet been made final by USP. A measuring cap (5 mL) was used during clinical studies; however, no cap is included for the to-be-marketed product.

**CONCLUSIONS & RECOMMENDATIONS:**

The application is APPROVABLE from CMC perspective. The proposed expiration date of 36-month is supported by stability data submitted. The deficiencies listed should be forwarded to the applicant.

  
Mamta Gautam-Basak, Ph.D.  
Review Chemist

18/23/00

cc:

- Orig. NDA 21-159 (with attachments)
- HFD-540/Division File (with attachments)
- HFD-540/ProjMgr/Vlutwak (with attachments)
- HFD-540/PharmTox/KMainigi
- HFD-540/MedOffr/PHuene
- HFD-540/Chem/MGautambasak (with attachments)
- HFD-540/ChemTeamLdr/WHDeCamp
- HFD-540/DD/JWilkin

*with 8/24/00 entered into DFS*

**List of Attachments:**

1. Flow Chart of Manufacturing Process for Drug Product (1 page)
2. Summary of the shelf-life estimation (data from primary stability batches)  
With statistical graphs (5 pages)
3. E-mails dated 8/10/00, 8/14/00, 8/17/00 regarding Micro Specifications (4 pages)

**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*26 pages*

JUN 21 2000

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS  
HFD-540

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-159 CHEM.REVIEW #: 2 REVIEW DATE: 18-MAY-2000

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	31-AUG-1999	01-SEP-1998	21-SEP-1998

NAME & ADDRESS OF APPLICANT: Medicis Pharmaceutical Corporation  
4343 East Camelback Road  
Phoenix, AZ 85016

Joseph P. Cooper  
Senior Vice President

DRUG PRODUCT NAME

<u>Proprietary:</u>	Loprox Shampoo 1%
<u>Nonproprietary/USAN:</u>	Ciclopirox
<u>Code Names/#'s:</u>	
<u>Chemical Type/</u>	Pyridinone
<u>Therapeutic Class:</u>	3S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL  
CATEGORY/INDICATION:

For the treatment of seborrheic dermatitis of  
the scalp and \_\_\_\_\_

DOSAGE FORM:

Shampoo

STRENGTHS:

1.0%

ROUTE OF ADMINISTRATION:

Topical

DISPENSED:

Rx  OTC

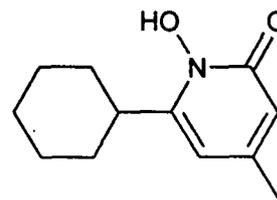
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.  
WT.:

6-Cyclohexyl-1-hydroxy-4-methyl-2-(1H)pyridinone

Molecular Formula: C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>

Molecular Weight: \_\_\_\_\_

CAS Number: [29342-05-0]



SUPPORTING DOCUMENTS:

CONSULTS: N/A

**REMARKS/COMMENTS:**

The proposed labeling for the drug product is the subject of this review. Other sections of the NDA are being reviewed under Chemistry Review #1.

**CONCLUSIONS & RECOMMENDATIONS:** The labeling is acceptable.

Comments listed should be forwarded to the applicant. Copies of final printed labeling should be submitted for review.

*MS*  
\_\_\_\_\_  
Mamta Gautam-Basak, Ph.D.  
Chemist, HFD-540

*16/21/00*

cc:

Orig. NDA 21-159

HFD-540/Division

HFD-540/ProjMgr/VLutwak

HFD-540/PharmTox/KMainigi

HFD-540/MedOffr/PHuene

HFD-540/Chem/MGautambasak

HFD-540/ChemTeamLdr/WHDeCamp *MS 6/21/00*

**APPEARS THIS WAY  
ON ORIGINAL**

**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*9 pages*