

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-159

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 21-159

DATE: February 25, 2003

SPONSOR: Medicis Pharmaceutical Corp.
Scottsdale, AZ

DRUG: Loprox (ciclopirox) Shampoo 1%

DATE OF AMENDMENT: February 14, 2003

REASON FOR AMENDMENT: Submission of final revised labeling

In response to our provision of draft labeling for Loprox shampoo on February 7, 2003, the sponsor submitted revised labeling on February 8, 2003. A teleconference was held on February 14, and in response the sponsor has further revised the label in accordance with our recommendations.

Reviewer's evaluation: The labeling submitted on February 14, 2003, is in accordance with our recommendations in the teleconference of February 14 on their labeling which was submitted on February 8, 2003. (A minor editorial note - a period should be placed at the end of the last sentence under ADVERSE REACTIONS.)

Conclusions: The application is approvable with the labeling submitted on February 14, 2003.

Phyllis A. Huene, M.D.

cc: HFD-540/Wilkin
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n21159.1b1

HFD-540 Trac No: 0211304
Document ID: AZ

Correspondence date: August 29, 2002
CDER Stamp date: September 3, 2002

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 21-159
MAJOR AMENDMENT

DATE: February 4, 2003

SPONSOR: Medicis Pharmaceutical Corp.
Scottsdale, AZ

DRUG: Loprox (ciclopirox) Shampoo 1%

PROPOSED INDICATION: Seborrheic dermatitis of the scalp.

REASON FOR ADDENDUM: Review of safety update

The sponsor has provided a summary of the Periodic Safety Update Reports that have been submitted to the regulatory authorities by Medicis and Aventis as of July 31, 2002. This includes all adverse event information received since October 1, 1989 by the Global Drug Surveillance and Pharmacology Department from clinical and post-marketing studies as well as from spontaneous reports, including adverse events published in the medical literature.

Ciclopirox was first marketed in Argentina in 1975, and is now marketed in 70 countries under various brand names. There have been no rejections of applications, suspensions or restrictions of distribution for safety reasons.

The available forms are 1% ciclopirox olamine cream and lotion for dermatomycoses, cutaneous candidiasis, and tinea versicolor; 0.77% ciclopirox gel for dermatomycoses and seborrheic dermatitis of the scalp, and 8% ciclopirox nail gel for onychomycosis.

Since 1989, 227 spontaneous adverse event reports in 184 patients have been received for the cream, lotion, and gel formulations. Since the last submission of the ISS in August 1999 three patients have reported serious adverse events. One patient reported peeling of the skin from the penis and scrotum, with skin hemorrhage, pain with urination, scrotal dermatitis, and balanoposthitis. One patient reported bullous contact dermatitis and application site erythema and edema. A third patient reported intertriginous eczematization of the feet.

Since 2000, 477 spontaneous adverse events in 347 patients have been received for the nail lacquer. The most frequently reported events were lack of drug effect, nail discoloration, other nail disorders, burning, numbness, pain, redness, and edema. Five serious adverse

events were reported; these were chest pain and shortness of breath in one, chemical keratoconjunctivitis, blurred vision and transient vision loss due to 'drug misuse' in one, severe chronic hives with swelling of the face in one, blood clot (not otherwise specified) in one, purple discoloration of the toe with toenail ulceration, redness extending to the ankle, and nausea in one, and epileptic seizure in one.

The most frequently reported adverse events were allergic reaction, rash, contact dermatitis, burning sensation, pruritus, eczema, lack of effect or aggravation, nail disorder, and vasodilation. With the exception of contact dermatitis, these events are reflected in the product labeling. Other singular unlabeled adverse events were also reported.

Ten case reports were classified as serious, as follows.

1. Accidental oral dose of 30 drops of Loprox lotion in an 8 year old child, resulting in nephrotic syndrome with anuria for 24 hours, and edema for 48 hours, with later total resolution.
2. Contact dermatitis requiring hospitalization, with complete recovery. The product was not specified.
3. Loss of circulation and swelling of the hands with ciclopirox nail lacquer; final outcome is unknown.
4. Allergic reaction, not further specified, after use of ciclopirox, requiring hospitalization. Recovery was complete, and patch test was positive for ciclopirox and benzyl alcohol.
5. Pain and numbness of the leg after accidental application of the nail lacquer to an infected area of the foot.
6. 'Serious eczema'; insufficient information was provided.
7. Erythroderma, edema, and desquamation of large sheets of epidermis in a patient treated for intertriginous mycosis with ciclopirox and terbinafine. The condition improved on topical steroids and permanganate baths.
8. Acute eczema on the extremities in a patient treated with Loprox cream. Skin tests were positive for Loprox and a number of other topical products.
9. Contact eczema in a patient treated with Loprox cream for an infected varicose ulcer. Patch test was positive for Loprox cream.
10. Allergic contact dermatitis of the hands and lower extremities with use of ciclopirox nail lacquer. Patch test was positive with the nail lacquer.

Reviewer's evaluation: There are no new adverse event data in the Safety Update which would change the evaluation that the product is safe and effective for the treatment of seborrheic dermatitis of the scalp, when used as prescribed, or that would change the information in the proposed package insert.

Phyllis A. Huene, M.D.

cc: HFD-540/Wilkin
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/s/

Phyllis Huene
2/11/03 09:11:35 AM
MEDICAL OFFICER

Markham Luke
2/13/03 01:10:09 PM
MEDICAL OFFICER
MO Review of Safety Update. Agree with MO conclusion.

Jonathan Wilkin
2/25/03 06:26:23 PM
MEDICAL OFFICER

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CDER Stamp date: September 3, 2002

MEDICAL OFFICER'S REVIEW OF NDA 21-159
MAJOR AMENDMENT

DATE: January 22, 2003

SPONSOR: Medicis Pharmaceutical Corp.
Scottsdale, AZ

DRUG: Loprox (ciclopirox) Shampoo 1%

PROPOSED INDICATION: Loprox shampoo is indicated for the topical
treatment of seborrheic dermatitis of the scalp in adults.

PROPOSED DOSAGE AND ADMINISTRATION: For treatment: applications twice
weekly for four weeks.

REASON FOR AMENDMENT: Response to the deficiencies noted in the
September 6, 2000, Not Approvable letter.

RELATED APPLICATION:

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Executive summary

- 1) Recommendations: It is recommended that the application be approved for the proposed labeling indication, namely, for the topical treatment of seborrheic dermatitis of the scalp in adults, and for

Statement
Revised per
TL/DD 2-26-

- 2) Summary of clinical findings: In support of the indication, the sponsor has provided three Phase 3 studies; these are Studies 204, 3001, and 017.

- A. Study 204: This was a double blind, multicenter, randomized comparison of Loprox shampoo at different frequencies of application with the vehicle in 177 patients with mild to pronounced seborrheic dermatitis of the scalp. The study was performed in Europe. Applications of Loprox shampoo were made once weekly, twice weekly, and three times weekly, and the vehicle was applied three times weekly, for four weeks.

The efficacy variables were scores for itching, scaling, and inflammation, based on scales of from 0 to 5. The protocol was amended after the study had been initiated to include a global evaluation of the status of the disease, but this was applied retroactively after some patients completed the study and so was not considered to be valid. The primary efficacy variable was determined to be the proportion of patients who were 'Effectively Treated', which consisted of those patients who were 'Cleared' or 'Almost Cleared' at the end of treatment. Cleared was defined as a score of 0 for inflammation, scaling, and itching. Almost Cleared was defined as a score of 0 for inflammation, and scores of 0 for itching and scaling, or scores of 1 if the baseline score were 3 or greater.

Statistical analyses of the results of Study 204 showed no significant differences between Loprox shampoo once weekly, twice weekly, or three times weekly and the vehicle in the proportion of patients that were Effectively Treated. It was therefore concluded that this study had not demonstrated the effectiveness of Loprox shampoo for the labeling indication.

Adverse events which were considered to be possibly treatment related were pruritus in one patient treated once weekly and hair loss in one patient treated twice weekly with Loprox shampoo. No treatment related events occurred in the three times weekly Loprox patients.

- B. Study 3001: The initial treatment phase (Segment A) was a double blind, multicenter, randomized comparison of Loprox shampoo with the vehicle in 942 patients with moderate to severe seborrheic dermatitis of the scalp. The study was performed in Europe. Applications of Loprox shampoo were made once weekly and twice weekly, and the vehicle was applied twice weekly, for four weeks. In the prophylaxis phase (Segment B), those patients that

were considered to have responded during the treatment phase were treated in a double blind manner with Loprox shampoo once weekly or once every other week, or with the vehicle once weekly, for an additional twelve weeks.

In Segment A the efficacy variables were scores for itching, scaling, and inflammation, based on scales of from 0 to 5, and an investigator's global evaluation of the status of the disease as none to severe, on a scale of from 0 to 5. The primary efficacy variable was a 'Primary Response', defined as a score of 0, or a score of 1 if the baseline score was 3 or greater, to be met simultaneously by the global status, inflammation and scaling at endpoint.

The results in Segment A showed that Loprox shampoo administered once weekly or twice weekly for four weeks was significantly superior to the vehicle in the rate of Primary Response. The proportion of patients with a Primary Response was 46% in the Loprox once weekly group, 59% in the Loprox twice weekly group, and 32% in the vehicle group. It was concluded that Segment A of the study adequately demonstrated the effectiveness of Loprox shampoo once weekly or twice weekly in the treatment of seborrheic dermatitis of the scalp.

In Segment B the primary efficacy variable was the relapse rate, defined as the worsening of the condition by 2 or more points on the global evaluation scale of from 0 to 5.

The results in Segment B showed that Loprox shampoo administered once weekly or once every other week for 12 weeks was significantly superior to the vehicle in the rate of relapse. The proportion of patients that had a relapse was 15% in the once weekly Loprox group, 22% in the once every other week Loprox group, and 35% in the vehicle group. It was concluded that Segment B of the study adequately demonstrated the effectiveness of Loprox shampoo once weekly and once every other week in the prevention of relapse in those patients that had responded to four weeks of active treatment.

Adverse events in Segment A were minor dermatological events of the scalp, such as pruritus, rash, dry skin, and alopecia, in 1% or less in all treatment groups. Adverse events were similar in Segment B.

- C. Study 00-017: This study has been provided in this amendment to the NDA, and is a double blind, multicenter, randomized comparison of Loprox shampoo with its vehicle in 499 patients with mild or more severe seborrheic dermatitis of the scalp. Treatment was administered twice weekly for four weeks.

The efficacy parameters were scores for erythema, scaling, and the global status of the seborrheic dermatitis, which were graded at biweekly intervals on scales of from 0 to 5. The primary efficacy variable was the proportion of patients that were 'Effectively Treated', defined as having a score of 0 (none), or a score of 1 (slight) if the baseline score were 3 or

greater, for scaling, erythema, and global status.

Results of the statistical analysis showed that Loprox shampoo was significantly superior to the vehicle in the proportion of patients that were Effectively Treated. It is concluded that Study 017 has adequately demonstrated the effectiveness of Loprox shampoo in the treatment of seborrheic dermatitis of the scalp, when administered twice weekly for four weeks.

Adverse events were similar to those in the other studies consisting of minor local dermatological effects in a few patients.

Review of original submission

NDA 21-159 was originally submitted on August 30, 1999 for the indication 'for the topical treatment and prevention of recurrence of seborrheic dermatitis of the scalp and its minor form, dandruff, in adults.' The proposed DOSAGE AND ADMINISTRATION was applications of 5-10 ml once or twice weekly for 4 weeks for treatment, and

The results of Phase 1 studies on local tolerance, sensitization, phototoxicity, and photosensitization were considered by the reviewer to show that Loprox shampoo has a low potential for irritation under the intended conditions of use, and little or no potential for sensitization, phototoxicity, or photosensitization.

The pivotal Phase 3 studies were Studies # 204 and 3001. Reference is made to the conduct and results of these studies described under the Executive Summary above. The results of the statistical analyses for Study 3001 were as follows.

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Primary Response rate - Segment A Study 3001			
	Ciclopirox QW	Ciclopirox BIW	Vehicle
Responders	171 (45.5%)	220 (58.5%)	60 (31.6%)

p values - Primary response rate	
Comparison	p value
Ciclopirox QW vs vehicle	0.0008
Ciclopirox BIW vs vehicle	<0.0001

Relapse rate - Segment B Study 3001			
	Ciclopirox QW n=136	Ciclopirox QOW n=145	Vehicle n=140
Relapse	20 (14.7%)	32 (22.1%)	49 (35.0%)

p values - relapse rate	
Comparison	p value
Ciclopirox QW vs vehicle	0.0001
Ciclopirox QOW vs vehicle	0.0149

The overall conclusion was that Study 3001 had adequately demonstrated the effectiveness for the proposed labeling indication, but that Study 204 had not demonstrated a similar effectiveness. It was felt that an additional clinical study was needed to support the results of Study 3001.

Not Approvable letter of 9/6/00

The deficiencies were summarized in the Not Approvable letter as follows.

'The sponsor needs to submit an adequate and well-controlled study to demonstrate the effectiveness of ciclopirox shampoo for the proposed labeling. Because there may be differences in populations, organisms, medical and/or hair care practices in Europe compared to the United States, it is recommended that this study either be performed in the United States or that the applicability of the study outcomes to the U.S. population, organisms, medical and/or hair care practices be documented.'

The letter further stated that, although not the basis for the Not Approvable action for the application, the following clinical issues should be addressed in the resubmission.

1. A rationale for the applicability of the clinical efficacy data collected in the European clinical studies and organisms studied to the US population and US medical practice.
2. Subset analyses of patients with dandruff, HIV infection, non-scalp seborrheic dermatitis, and different racial heritage.
3. An explanation of the results of Study 3001, in which there was a higher disease relapse rate in the once per four day treatment arm than in the once per seven day treatment arm.

Review of SPA request

In response to the Not Approvable letter, a request for a Special Protocol Assessment was submitted on 12/28/00 for Protocol 00-017. The sponsor subsequently revised the protocol in accordance with the Agency's comments, and was advised on 7/9/01 that the revised protocol was satisfactory from a clinical standpoint. Study MED 00-017, provided in this amendment to NDA 21-159, was conducted in accordance with the revised protocol.

Pre-NDA telecon of 3/11/02

In this meeting the Agency felt that the proposed structure and format of the NDA amendment, as specified by the sponsor, were acceptable; this included the Integrated Summary of Safety, the Integrated Summary of Safety, the clinical data listings and tabulations, and the electronic filing. Questions regarding a proposed discussion in the amendment of clinical deficiencies in the Not Approvable letter were deemed to be review issues which would not be addressed in the telecon.

An additional clinical issue discussed involved the provision of updated clinical information. It was stated that the sponsor will

provide information on all studies and uses of the drug, but proposes to provide this only on the shampoo and not for other approved dosage forms. The Agency responded that this is not acceptable; such information as is available should be submitted on all dosage forms of ciclopirox.

Financial disclosure statement

The sponsor has provided the following statement.

'As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).'

Listed are all the investigators for Study MED 0017.

Pediatric waiver request

The sponsor was granted a waiver of pediatric studies on 9/8/00 in the review of the original submission of NDA 21-159. This stated:
'Pediatric studies are not needed because the drug product ciclopirox shampoo, 1%, would not offer a meaningful therapeutic benefit over existing treatments for pediatric patients, and is not likely to be used in a substantial number of pediatric patients. Cradle cap would be a separate indication. Cradle cap is NOT identical to seborrheic dermatitis or dandruff. Seborrheic dermatitis and dandruff appear with puberty. The database that is satisfactory for demonstrating efficacy and safety for those over 18 years of age should be extrapolatable down to the age of first appearance of seborrheic dermatitis/dandruff.'

The waiver is in effect for the current submission.

Study MED 00-017

The study was performed with the to-be-marketed formulation, and was initiated in November 2001 and completed in April 2002. The investigators were as follows.

Debra Breneman, M.D. Dermatology Clinical Research Center Cincinnati, OH	Mark Ling, M.D. MedaPhase, Inc. Newman, GA
Alicia Bucko, M.D. Academic Dermatology Associates Albuquerque, NM	Amy McMichael, M.D. Wake Forest University School of Medicine Winston-Salem, NC
Zoe Draelos, M.D. Dermatology Consulting Services High Point, NC	Steven Mings, M.D. Radiant Research Boise, ID
Eoni Elewsky, M.D. University of Alabama Birmingham, AL	Christopher Nelson, M.D. Radiant Research St. Petersburg, FL
J. John Goodman, M.D. Radiant Research West Palm Beach, FL	Jerold Powers, M.D. Radiant Research Scottsdale, AZ
Jo Lynne Herzog, M.D. Radiant Research Birmingham, AL	Phoebe Rich, M.D. Northwest Cutaneous Research Specialists Portland, OR
Janet Hickman, M.D. The Education and Research Foundation Lynchburg, VA	Toivo Rist, M.D. Dermatology Associates of Knoxville Knoxville, TN
Mark Lebwohl, M.D. Mount Sinai School of Medicine New York, NY	Ted Rosen, M.D. Baylor dermatology Houston, TX
Jack Leshner, M.D. Medical College of Georgia Augusta, GA	Mary Patrice Sheehan, M.D. Ntouch Research Corp Pittsburgh, PA
Guy Webster, M.D. Jefferson Medical College Philadelphia, PA	Kenneth Stein, M.D. Radiant Research Santa Rosa, CA

- 1) Study title: A Vehicle-controlled, Randomized, Double-blind, Multicenter Study of the Efficacy and Safety of 1% Ciclopirox Shampoo in the Treatment of Seborrheic Dermatitis of the Scalp.
- 2) Study objective: The primary objective of the study was to assess the efficacy of 1% ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp in a study conducted within the US. The secondary objective was to assess the safety and tolerability of 1% ciclopirox shampoo during the treatment of seborrheic dermatitis of the scalp.

- 3) Study design: This was a double blind, randomized, multicenter comparison of 1% ciclopirox shampoo with the shampoo vehicle in patients with seborrheic dermatitis of the scalp, with applications twice weekly for 4 weeks.
- 4) Inclusion criteria: Patients were eligible for inclusion in the study if the following criteria were met.
 - a. Males or females, age 16 years or more, in good physical health.
 - b. A diagnosis of stable or exacerbating seborrheic dermatitis of the scalp (chronically recurring for at least 6 months), as evidenced by a score of 2 or greater for erythema, scaling, and 'status of seborrheic dermatitis'. The scoring scales are described below under 'Efficacy parameters'; a score of 2 denotes a mild condition.
- 5) Exclusion criteria: Patients with the following were excluded from enrollment in the study.
 - a. Psoriasis of any type, anywhere on the body.
 - b. History of atopic dermatitis.
 - c. Topical treatment of the scalp with other antifungal medication, including ciclopirox, or with corticosteroids in the 4 weeks before start of randomized treatment.
 - d. Topical treatment of the scalp in the 2 weeks before start of randomized treatment with medication containing any of the following: tar, selenium sulfide, zinc pyrithione, salicylic acid, sulfur.
 - e. Systemic use of corticosteroids, retinoids, erythromycin, tetracycline, or any of its derivatives (e.g. minocycline hydrochloride, doxycycline) trimethoprim/sulfamethoxazole, cytostatic or immunomodulating drugs, or any other antimycotic within the 4 weeks before the start of randomized treatment.
 - f. A likelihood of requiring treatment during the study period with drugs not permitted by the study protocol.
 - g. Asthma requiring regular treatment with more than 800 ug corticosteroids of inhaler therapy.
 - h. A history of hypersensitivity to the study medication or to drugs with similar chemical structure.
 - i. Uncontrolled diabetes.
 - j. Clinical signs and/or history of immunosuppression.
 - k. Abnormal baseline findings considered by the investigator to be indicative of conditions that might affect the study results.
 - l. Severe disease likely to jeopardize the planned termination of the study, e.g., cancer, cardiac infarct, unstable angina pectoris.
 - m. Pregnancy, lactation, childbearing potential without adequate contraception. (Adequate contraceptive methods included oral contraceptives and implants.)
 - n. Treatment with any other investigational drug in the 4 weeks before study entry.
 - o. History of Parkinson's disease.
 - p. History of drug or alcohol abuse.
 - q. History or suspicion of unreliability, poor co-operation or non-compliance with medical treatment.

- r. A mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study.
- 6) Treatment regimen: Applications were made twice weekly for 4 weeks. With a time interval of 3 to 4 days between applications. Patients were permitted to perform extra hair washes as desired with a non-medicated shampoo; for these, — shampoo was supplied.

Each application comprised 5 ml of test product, or 10 ml for those with longer than shoulder length hair, measured with a measuring spoon. The hair and scalp were first wetted, followed by lathering and thorough massage of the scalp with the shampoo, which was allowed to take effect for a timer-controlled 3 minutes, and followed by rinsing. Contact of the shampoo with the eyes was to be avoided.

The following concomitant treatments were not permitted during the study.

- Retinoids, systemic or applied to the scalp.
 - Trimethoprim/sulfamethoxazole, cytostatic or immunomodulating drugs (systemic).
 - Erythromycin and all macrolide antibiotics (systemic or topical at or away from the scalp).
 - Tetracycline and all related derivatives (systemic or topical at or away from the scalp).
 - Corticosteroids (systemic or applied to the scalp).
 - Antimycotics (systemic or applied to the scalp).
 - Tar, selenium sulfide, zinc pyrithione, salicylic acid, sulfur (applied to the scalp).
- 7) Efficacy parameters. The patients were evaluated at baseline and at 2 and 4 weeks, as follows.
- a. Signs and symptoms. Erythema and scaling were scored on the following scales.

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Erythema		
Score	Severity	Description
0	None	
1	Slight	barely perceptible
2	Mild	slightly pink
3	Moderate	moderately pink
4	Pronounced	deep pink to red
5	Severe	deep red to severely red

Scaling		
Score	Severity	Description
0	None	
1	Slight	barely perceptible scale - small flakes resembling a coarse grayish powder
2	Mild	minimal to intermediate scale
3	Moderate	definite scale - large flakes very loosely attached to the scalp and forming an irregular whitish surface
4	Pronounced	prominent scale - flakes apparently congealed together into yellowish plates adhering to the scalp
5	Severe	excessive thick yellowish and crusted adherent scale.

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Itching was rated by the patient on the following scale.

Scaling	
Score	Severity
0	None
1	Slight
2	Mild
3	Moderate
4	Pronounced
5	Severe

- b. Investigator's global evaluation: The status of seborrheic dermatitis was scored on the following scale.

Status of seborrheic dermatitis		
Score	Severity	Description
0	None	
1	Slight	barely perceptible erythema and scale
2	Mild	slight erythema and minimal scale
3	Moderate	moderate erythema and moderate scale
4	Pronounced	pronounced erythema and pronounced scale
5	Severe	severe erythema and severe scale

- c. Percentage of scalp area affected: This was estimated by the investigator as follows.

0 - 10%
 >10 - 20%
 >20 - 30%
 >30 - 50%
 >50 - 75%
 >75 - 100%

- 8) Primary efficacy variable: The primary efficacy variable was 'Effectively Treated', defined as a score of 0, or a score of 1 if the baseline score was 3 or greater, for scaling, erythema, and status of seborrheic dermatitis.

Secondary variables were as follows.

Secondary efficacy variables	
Variable	Definition
Cleared	Score of 0 for disease status, erythema, scaling, and itching.
Improved 1	Improvement from baseline by 2 points or more for disease status, erythema, and scaling.
Improved 2	Score of 1 or less, or improvement from baseline of 3 or more points, in disease status.
Scaling response	Score of 0, or score of 1 if the baseline score was 3 or greater, for the respective sign.
Erythema response	As for scaling response
Itching response	As for scaling response
Sumscore	Sum of scaling, erythema, and itching scores.

- 9) Safety evaluation: Adverse events, observed by the investigator or reported by the patient, were documented, together with an assessment of severity and causality. Any deterioration of the seborrheic dermatitis of 2 or more points on the scale for the status of the seborrheic dermatitis was to be regarded as an adverse event.

A subset of patients from five centers had the following assessments of hematology and clinical chemistries: Hgb, Ht, RBC, creatinine, SGOT, SGPT, GGT, cholesterol, triglycerides, and urinalyses.

Results of the study were as follows.

- 1) Patient enrollment and demographic characteristics: 499 patients were enrolled into the study, of which 250 were in the ciclopirox group and 249 were in the vehicle group. Demographic characteristics and baseline disease severity were as follows.

Demographic characteristics Study 017		
	Ciclopirox n=250	Vehicle n=249

Race		
Caucasian	195 (78%)	205 (82%)
Black	28 (11%)	21 (8%)
Asian	5 (2%)	2 (1%)
Hispanic	18 (7%)	18 (7%)
Other	4 (2%)	3 (1%)
Gender		
Male	115 (46%)	122 (49%)
Female	135 (54%)	127 (51%)
Age		
< 40	94 (38%)	91 (37%)
40-64	116 (46%)	117 (47%)
>= 65	40 (16%)	40 (16%)
Severity		
Mild	54 (22%)	49 (20%)
Moderate	166 (66%)	174 (70%)
Severe	30 (12%)	26 (10%)

2) Patient disposition: Patients were prematurely terminated from the study for the following reasons.

	Ciclopirox	Vehicle
Adverse event	2	3
Patient request	4	1
Non compliance	1	5
Lost to followup	5	3
Protocol violation	3	1
Other	2	1
Total	17	14

3) Efficacy evaluation: Primary efficacy variable. The following evaluations were done on the ITT population, defined as all patients randomized and dispensed study medication.

The proportion of patients that were 'Effectively Treated', defined as having a score of 0, or a score of 1 if the baseline score was 3 or greater, for disease status, scaling, and erythema, was as follows.

Effectively Treated Study 017

Ciclopirox BIW n=250	Vehicle n=249	p value
65 (26.0%)	32 (12.9%)	0.0001

Subgroup analyses of the primary efficacy variable by gender, race, age, and the presence of non-scalp dermatitis were as follows.

Effectively Treated - subgroup analyses Study 017		
	Ciclopirox BIW n=250	Vehicle n=249
<u>Race</u>		
Caucasian	50 (26%)	20 (10%)
Black	3 (11%)	5 (24%)
Other	12 (44%)	7 (30%)
<u>Gender</u>		
Male	33 (29%)	17 (14%)
Female	32 (24%)	15 (12%)
<u>Age</u>		
< 40	23 (25%)	12 (13%)
40-64	35 (30%)	15 (13%)
>/= 65	7 (18%)	5 (13%)
Non-scalp dermatitis	15 (18%)	11 (12%)

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- 4) Efficacy evaluation: Secondary efficacy variables. The following analyses were done on the ITT population.

Secondary efficacy variables Study 017			
	Ciclopirox BIW n=250	Vehicle n=249	p value
Cleared ^a	25 (10%)	8 (3%)	0.0017
Improved 1 ^b	72 (29%)	38 (15%)	0.0001
Improved 2 ^c	106 (42%)	60 (24%)	< 0.0001
a. Cleared = score of 0 for disease status, scaling, erythema, itching b. Improved 1 = improvement by ≥ 2 for disease status, scaling, erythema c. Improved 2 = improvement by ≥ 3 for disease status			

Clinical signs and symptoms Study 017			
	Ciclopirox BIW n=250	Vehicle n=249	p value
Scaling response ^a	85 (34%)	50 (20%)	0.0002
Erythema response ^b	98 (39%)	51 (21%)	< 0.0001
Itching response ^c	120 (48%)	74 (30%)	< 0.0001
Sumscore ^d improvement from baseline	3.8	2.5	< 0.0001
a. Scaling response = score of 0, or 1 if ≥ 3 at baseline b. Erythema response = score of 0, or 1 if ≥ 3 at baseline c. Itching response = score of 0, or 1 if ≥ 3 at baseline d. Sumscore = sumscore of erythema, itching, scaling			

Status of seborrheic dermatitis Study 017				
	Ciclopirox BIW n=250		Vehicle n=249	
	Baseline	Endpoint	Baseline	Endpoint
None	0	33 (13%)	0	15 (6%)
Slight	0	72 (29%)	0	44 (18%)
Mild	69 (28%)	81 (32%)	67 (27%)	73 (29%)
Moderate	139 (56%)	46 (18%)	134 (54%)	94 (38%)
Pronounced	38 (15%)	15 (6%)	44 (18%)	21 (8%)
Severe	4 (2%)	3 (1%)	4 (2%)	2 (1%)

- 5) Safety evaluation. The adverse events of the skin and appendages which occurred in more than 1% of patients were as follows.

Adverse events Skin and appendages - of greater than 1% incidence		
	Ciclopirox BIW n=250	Vehicle n=249
Hair texture abnormal	3 (1%)	-
Pruritus	7 (3%)	8 (3%)
Seborrhea	3 (1%)	4 (2%)
Skin exfoliation	-	5 (2%)
Application site reaction	1 (0.4%)	4 (2%)

The listing of all patients with skin and appendages adverse events by preferred terms, regardless of frequency, was as follows.

Adverse events Skin and appendages - all occurrences		
	Ciclopirox BIW n=250	Vehicle n=249
Alopecia	1 (0.4%)	1 (0.4%)
Contact dermatitis	1 (0.4%)	-
Exfoliative dermatitis	-	2 (0.8%)
Fungal dermatitis	-	1 (0.4%)
Folliculitis	1 (0.4%)	-
Hair disorder NOS	-	1 (0.4%)
Hair texture abnormal	3 (1%)	-
Pruritus	7 (3%)	8 (3%)
Psoriasis	1 (0.4%)	1 (0.4%)
Rash	2 (0.8%)	-
Erythematous rash	-	1 (0.4%)
Pustular rash	-	2 (0.8%)
Seborrhea	3 (1%)	4 (2%)
Skin disorder	1 (0.4%)	-
Dry skin	-	1 (0.4%)
Skin exfoliation	-	5 (2%)
Localized skin reaction	-	1 (0.4%)
Urticaria	1 (0.4%)	-
Vesicular rash	1 (0.4%)	-

Treatment emergent adverse events of the skin and appendages, by preferred terms, which occurred in at least one patient in the ciclopirox group, were as follows.

Adverse events Skin and appendages - treatment emergent		
	Ciclopirox BIW n=250	Vehicle n=249
Pruritus	8 (3%)	8 (3%)
Hair disorder	3 (1%)	1 (0.4%)
Seborrhea	3 (1%)	3 (1%)
Alopecia	1 (0.4%)	1 (0.4%)
Contact dermatitis	1 (0.4%)	-
Psoriasis	1 (0.4%)	1 (0.4%)
Pustular rash	1 (0.4%)	2 (1%)
Rash	1 (0.4%)	1 (0.4%)
Skin disorder	1 (0.4%)	1 (0.4%)
Urticaria	1 (0.4%)	-
Vesicullóbullous rash	1 (0.4%)	-

One patient treated with ciclopirox shampoo was withdrawn from the study due to continuous mild pruritus at the application site on day 1; this was considered to be probably related to the study medication. One vehicle patient was withdrawn from the study on day 6 due to moderate worsening of the seborrheic dermatitis, and another vehicle patient was withdrawn on day 15 because of scalp psoriasis.

There were no clinically significant mean changes in laboratory parameters. Six patients had predefined abnormal changes in laboratory values, including five ciclopirox patients and 1 vehicle patient. The abnormalities in the ciclopirox group consisted of elevated triglycerides in 1, decreased triglycerides in 1, elevated GGT in 1, elevated total cholesterol in 1, and decreased hemoglobin, hematocrit, and RBC in 1. The vehicle patient had an elevated SGOT.

Reviewer's evaluation - Study 017: In the primary efficacy variable, defined as a score of 0, or a score of 1 if the baseline score was 3 or greater, for scaling, erythema, and global status, ciclopirox shampoo administered twice weekly was significantly superior to the vehicle at endpoint after four weeks of treatment. It is felt that this study demonstrates the effectiveness of ciclopirox shampoo 1% in the treatment of seborrheic dermatitis of the scalp, when administered twice weekly for four weeks.

Summary of efficacy - Studies 3001 and 017

The results for the primary efficacy variable in the pivotal Studies 3001 and 017, defined as the proportion of patients with a score of 0, or a score of 1 if the baseline score was 3 or greater, for global status, scaling, and erythema, in those patients treated twice weekly, was as follows. (This was termed 'Effectively Treated' in Study 017, and 'Primary Response' in Study 3001. Also 'erythema' in Study 017 was termed 'inflammation' in Study 3001.)

Primary Response Study 3001		
Ciclopirox BIW	Vehicle	p value
220 (58.5%)	60 (31.6%)	< 0.0001

Effectively Treated Study 017		
Ciclopirox BIW n=250	Vehicle n=249	p value
65 (26.0%)	32 (12.9%)	0.0001

Summary of safety - Studies 3001 and 017

During the review of this submission the sponsor was requested to provide the patient data listings of adverse events for the skin and appendages as described in the original (verbatim) terms on the case report forms, together with the preferred terms, for Studies 3001 and MED 0017. The sponsor provided this information in their submission of November 21, 2002. These verbatim adverse events were compiled by this reviewer, with omission of those events that were obviously not treatment-related, as follows.

Adverse events - verbatim terms Studies 3001 and 017 Ciclopirox BIW n=626	
Adverse event	# pts
seborrheic dermatitis	1
hair discoloration	1
itching after use	2
scaling	1
itching of scalp	2
erythema of scalp	2
vesiculobullous rash	1
exacerbation of seborrheic dermatitis	2
papules on scalp	1
redness after application	1
otitis externa	1
facial eczema	2
acne	1
seborrheic dermatitis, scalp and ears	1
increased itching	6
coarse hair	1
psoriasis	1
hair loss	1
burning during application	1
seborrheic derm face	1
worsening of seborrheic dermatitis	1
increased dryness of hair	1
dry pruritic patches on face	1
flare of seb derm of face	1
blister on scalp	1

dry brittle hair	1
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Adverse events - verbatim terms Studies 3001 and 017 Vehicle n=439	
Adverse event	# pts
seborrheic dermatitis	2
irritation of hands	1
furuncle	1
furuncle ear	1
pruritus scalp	4
worsening of seborrheic dermatitis	4
worsening of facial seborrheic dermatitis	1
seborrheic eczema of face/ears	2
pruritus	1
intolerance	1
erythema and pruritus, neck and face	1
increased scalp scale	6
increased scalp itching	5
worsening of seborrheic dermatitis	2
tingle of scalp after application	1
pustules	2
burning during application	1
scratch marks scalp	1
dry face	1
hair loss	1
burning across hairline after use of study shampoo	1
tightness of scalp	1

scaling behind ears

1

Statistical review

Dr. Kathleen Fritsch has found that the sponsor has demonstrated a statistically significant effect for ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp in two studies for twice weekly treatment for four weeks, using 'Effective Treatment' as the primary efficacy endpoint, defined as a score of 0, or a score of 1 if the baseline score were 3 or greater, for global status, erythema, and scaling. Prophylactic treatment with ciclopirox shampoo has been studied and demonstrated to be effective in only a single study.

Response to Not Approvable letter

The deficiencies stated in the Not Approvable letter were as follows:

'The sponsor needs to submit an adequate and well-controlled study to demonstrate the effectiveness of ciclopirox shampoo for the proposed labeling. Because there may be differences in populations, organisms, medical and/or hair care practices' in Europe compared to the United States, it is recommended that this study either be performed in the United States or that the applicability of the study outcomes to the U.S. population, organisms, medical and/or hair care practices be documented.'

Reviewer's comments: The sponsor has provided in this submission an additional controlled study, Study 00-017, which was performed in the U.S. population. It is felt that this study demonstrates the effectiveness for the treatment of seborrheic dermatitis of the scalp, and that this requirement has been satisfied.

The letter further stated that, although not the basis for the Not Approvable action for the application, the following clinical issues should be addressed in the resubmission.

1. A rationale for the applicability of the clinical efficacy data collected in the European clinical studies and organisms studied to the US population and US medical practice.

Reviewer's comments: It is felt that the applicability of the European clinical efficacy data to the U.S. population has been demonstrated by the results of Study 00-017, which was performed in the U.S., and that this requirement (issue # 1) has been satisfied.

2. Subset analyses of patients with dandruff, HIV infection, non-scalp seborrheic dermatitis, and different racial heritage.

Reviewer's comments: Subset analyses on the basis of race and the

presence of non-scalp seborrheic dermatitis have been provided. The sponsor explains that since no patients with dandruff alone were selected in these studies, no such analysis is possible. In regard to those with HIV infection, patients with clinical signs or a history of immunosuppression were excluded from the pivotal studies 3001 and 017, and the sponsor had felt that HIV screening was unacceptable for ethical reasons. Therefore no subset analysis could be performed on patients with HIV infection. It is felt that this requirement (issue # 2) has been satisfactorily addressed.

3. An explanation of the results of Study 3001, in which there was a higher disease relapse rate in the once per four day treatment arm than in the once per seven day treatment arm.

Reviewer's comments: This requirement in the Not Approvable letter was apparently in error. The active treatment groups in the prophylaxis segment of Study 3001 were Loprox once weekly (QW) and Loprox once every other week (QOW). The relapse rate was higher in the QOW group (22%) than in the QW group (15%), as would be expected. There is therefore no need for the sponsor to respond to this request.

Summary and evaluation: This amendment to NDA 21-159 provides an additional clinical study, Study 00-017, which was performed in the U.S., and was undertaken to demonstrate the safety and effectiveness of Loprox shampoo 1% in the treatment of seborrheic dermatitis of the scalp. This was a double blind, multicenter, randomized comparison of Loprox shampoo with its vehicle in 499 patients with mild or more severe seborrheic dermatitis of the scalp. Treatment was administered twice weekly for four weeks.

The efficacy parameters were scores for erythema, scaling, and the global status of the seborrheic dermatitis, which were graded at biweekly intervals on scales of from 0 to 5. The primary efficacy variable was the proportion of patients that were 'Effectively Treated', defined as having a score of 0 (none), or a score of 1 (slight) if the baseline score were 3 or greater, for scaling, erythema, and global status.

Results of the statistical analysis showed that Loprox shampoo was significantly superior to the vehicle in the proportion of patients that were Effectively Treated. It is concluded that Study 017 has adequately demonstrated the effectiveness of Loprox shampoo in the treatment of seborrheic dermatitis of the scalp, when administered twice weekly for four weeks.

A subset analysis by race indicated less effectiveness in black patients; however, the sample size was too small for a valid comparison.

Adverse events were minor local dermatological effects in a few patients.

The results of Study 3001, provided in the original submission of the NDA, have also demonstrated the safety and effectiveness of Loprox shampoo for the treatment of seborrheic dermatitis of the scalp, when administered twice weekly for four weeks.

The results of Study 3001 have demonstrated the safety and effectiveness of Loprox shampoo for the prevention of recurrence of seborrheic dermatitis of the scalp, when administered once weekly or once every other week for 12 weeks. These results, however, have not been duplicated in a second study.

Conclusions: It is felt that the safety and effectiveness of Loprox shampoo 1% has been adequately demonstrated for the treatment of seborrheic dermatitis of the scalp, but not for _____ of seborrheic dermatitis of the scalp. An additional study on _____ is needed to demonstrate the effectiveness for this indication.

Recommendations: It is recommended that Loprox shampoo 1% not be approved for the proposed labeling indication. With appropriately revised labeling, Loprox shampoo is approvable for the treatment of seborrheic dermatitis of the scalp, but not for _____

Phyllis A. Huene, M.D.

cc: HFD-540/Wilkin
HFD-540/Luke
HFD-540/Huene
HFD-540/Fritsch
HFD-540/Alosh
HFD-540/Smith

n21159.az

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this page is the manifestation of the electronic signature.**

/s/

Phyllis Huene
1/27/03 10:37:51 AM
MEDICAL OFFICER

Markham Luke
1/28/03 11:46:04 AM
MEDICAL OFFICER
Agree with MO recommendations, which will be incorporated into
labeling.

Jonathan Wilkin
2/25/03 06:21:50 PM
MEDICAL OFFICER
The first paragraph under Exec Summary on p3 is
not consistent with, and is superseded by, the
conclusions and recommendations on p26. Safety Update is
not addressed in this review and will be
considered in an amendment to the MOR.

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MEDICAL OFFICER'S REVIEW OF AMENDMENT TO IND
AMENDMENT # 21

DATE: February 12, 2001

SPONSOR: Medicis Pharmaceutical Corp.
Scottsdale, AZ

DRUG: Loprox (ciclopirox) shampoo 1%

PHARMACOLOGIC CATEGORY: Antifungal

PROPOSED INDICATION: Seborrheic dermatitis of the scalp.

DOSAGE FORM AND ROUTE OF ADMINISTRATION: Shampoo

REASON FOR AMENDMENT: Submission of a Phase 3 protocol in response to the non-approvable letter. (45 day Special Protocol)

RELATED NDA: NDA 21-159

REGULATORY BACKGROUND:

- a. Study phase 3
- b. Regulatory intent: To provide a protocol for an additional clinical study, to satisfy the requirements of the non-approvable letter.
- c. Date/type of previous meetings concerning this submission/protocol: None
- d. Principal investigator is not named.
- e. The IRB has not been named.
- f. Previous studies with this drug in humans have been carried out.

Background

A not approvable letter was issued on September 6, 2000 for NDA 21-159 for Loprox (ciclopirox) shampoo 1% in the treatment of seborrheic dermatitis. The clinical portion of the not approvable letter was as follows:

'The sponsor needs to submit an adequate and well controlled study to demonstrate the effectiveness of ciclopirox shampoo for the proposed labeling. Because there may be differences in

populations, organisms, medical and/or hair practices in Europe compared to the United States, it is recommended that this study either be performed in the United States or that the applicability of the study outcomes to the US population, organisms, medical and/or hair care practices be documented.

Although not the basis for the Not Approvable action for this application, the following issues should be addressed in the resubmission:

1. A rationale for the applicability of the clinical efficacy data collected in the European clinical studies and organisms studied to the US population and US medical practice.
2. Subset analyses of patients with dandruff, HIV infection, non-scalp seborrheic dermatitis, and different racial heritage.
3. An explanation of the results of Study 3001, in which there was a higher disease relapse rate in the once per four day treatment arm than in the once per seven day treatment arm.'

Review of NDA 21-159

The proposed labeling indication for Loprox shampoo is the topical treatment _____ of seborrheic dermatitis of the scalp and _____ in adults. Two pivotal Phase 3 studies were provided in support of the safety and effectiveness for this indication.

The pivotal Phase 3 studies were Studies # 204 and 3001. Study 204 was a controlled comparison of 1% Ciclopirox shampoo applied QW (once daily), BIW (twice daily), and TIW (three times daily) with the vehicle applied TIW for four weeks in 177 patients. The efficacy variables were scores for itching, scaling, and inflammation. (The protocol was amended after the study had been initiated to include a global evaluation of the status of the disease, but this was applied retroactively after some patients completed the study and so was not considered to be valid.) The primary efficacy variable was determined to be the proportion of patients who were 'Effectively Treated', which included those patients who were 'Cleared' or 'Almost Cleared' at the end of treatment. Cleared was defined as a score of 0 for inflammation, scaling, and itching. Almost Cleared was defined as a score of 0 for inflammation, and scores of 0 for itching and scaling, or scores of 1 if the baseline score were 3 or greater.

Statistical analyses of the results of Study 204 showed no significant differences between Ciclopirox shampoo QW, BIW, or TIW, and the vehicle in the proportion of patients that were Effectively Treated. It was therefore concluded that this study has not demonstrated the effectiveness of Loprox shampoo for the labeling indication.

Study 3001 was a controlled comparison of Ciclopirox shampoo QW and BIW and the vehicle BIW when applied for four weeks in 942 patients. This was followed by twelve weeks of treatment with Ciclopirox shampoo QW or QOW or the vehicle BIW in those patients who were considered to have responded during the first four weeks of treatment. The efficacy variables were scores for itching, scaling, and inflammation, and scores for the investigator's global evaluation of the status of the disease. The primary efficacy variable for the first four weeks of active treatment was the 'Primary Response', which was defined as scores of 0 for the global status, inflammation, and scaling, or scores of 1 if the baseline score were 3 or greater. The primary efficacy variable for the second part of the study, the twelve week prophylaxis phase, was the relapse rate, defined as the worsening of the condition by 2 or more points.

Results of statistical analyses in Study 3001 at the end of the four week active treatment period showed a significant superiority of Ciclopirox shampoo QW and BIW over the vehicle in the Primary Response rate. At the end of the twelve week prophylactic treatment period, Ciclopirox QW and QOW were significantly superior to the vehicle in the relapse rate. It was concluded that the results of this study adequately demonstrate the effectiveness of Ciclopirox shampoo QW and BIW in the treatment of seborrheic dermatitis, and the effectiveness of Ciclopirox shampoo QW and QOW in the — in those patients who have responded to the first four week active treatment period.

It was noted that several items that were discussed with the sponsor at the pre-NDA meeting had not been addressed or provided by the sponsor. These included:

- a. a demonstration of the applicability of the data and organisms studied to the US population and US medical practice.
- b. Subset analyses of patients with dandruff, HIV infection, non-scalp seborrheic dermatitis, and different racial heritage.

The conclusion was that the results of one of the two pivotal studies (#3001) has adequately demonstrated the effectiveness for the proposed labeling indication, but that the other study (#204) has not demonstrated a similar effectiveness. It was felt that an additional clinical study is needed which supports the results of Study 3001.

Protocol # 00-017

- 1) Study Title: A Vehicle-Controlled, Randomized, Double-Blind, Multicenter Study of the Efficacy and Safety of 1% Ciclopirox Shampoo in the Treatment of Seborrheic Dermatitis of the Scalp.
- 2) Study objective: This is to determine the efficacy and safety of 1% Ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp, in a study conducted within the US.
- 3) Study design: This is a double blind, randomized, multicenter comparison of 1% Loprox shampoo with the shampoo vehicle in patients with seborrheic dermatitis of the scalp, with applications twice weekly for four weeks.
- 4) Planned number of patients/centers: 400 patients at 15 centers in the US.
- 5) Inclusion criteria: Patients who meet the following criteria are to be enrolled into the study.
 - a. Males and females 18 years of age or older, in good physical health.
 - b. A diagnosis of stable or exacerbating seborrheic dermatitis of the scalp, as evidenced at screening and baseline by a score for 'status of seborrheic dermatitis' of 2 or greater, a score for scaling of 2 or greater, and a score for inflammation of 2 or greater, on a scale as described below under 'Efficacy parameters'. On this scale a '2' designates a mild condition.

If during the course of enrollment it is felt that an insufficient number of patients have scores of 3 or greater in the baseline assessments, the investigators may be instructed to further enroll only patients with a score of at least 3, corresponding to a moderate severity of dermatitis.

- 5) Exclusion criteria: Patients with the following are to be excluded from enrollment in the study.
- a. Psoriasis of any type at any location on the body.
 - b. History of atopic dermatitis.
 - c. Topical treatment of the scalp with other antifungal medication, including ciclopirox, or with corticosteroids in the four weeks before the start of treatment.
 - d. Systemic use of corticosteroids, retinoids, erythromycin, tetracycline or any of its derivatives (e.g., minocycline hydrochloride, doxycycline) trimethoprim/sulfamethoxazole, cytostatic or immunomodulating drugs, or any other antimycotic within the four weeks before the start of treatment.
 - e. Likelihood of requiring treatment during the study period with drugs not permitted in the study protocol.
 - f. Asthma requiring regular treatment with more than 800 ug corticosteroids of inhaler therapy.
 - g. History of hypersensitivity to the study medication or to drugs with similar chemical structure.
 - h. Uncontrolled diabetes.
 - i. Clinical signs and/or symptoms of immunosuppression.
 - j. Abnormal baseline findings considered by the investigator to be indicative of conditions that might affect study results.
 - k. Severe disease, likely to jeopardize the planned termination of the study, e.g., cancer, cardiac infarct, unstable angina pectoris.
 - l. Pregnancy, lactation, childbearing potential without adequate contraception.
 - m. Treatment with any other investigational drug in the four weeks before study entry.
 - n. History of Parkinson's disease.
 - o. Treatment with any other investigational drug in the 4 weeks before study entry.

6) Treatment regimen.

Applications of 1% ciclopirox shampoo and the shampoo vehicle will be made twice weekly for four weeks.

A two week washout period will precede the treatment period. The sponsor will provide ~~_____~~ shampoo to use during the washout period, or the patient may use another cosmetic shampoo from a list of acceptable shampoos provided by the sponsor. Shampooing is to be done at least twice weekly during the washout period.

During the treatment period applications of 5 ml, using a measuring jug, are to be made

in patients with shoulder length hair or shorter, or 10 ml in those patients with longer hair. After lathering and massage of the scalp, the shampoo is to remain for as close to 3 minutes as possible, using a timer, before rinsing.

There is to be a 3 to 4 day interval between applications of the test products, with applications made on the day before the return visits. — shampoo is to be used as desired between test product applications.

7) Efficacy parameters.

At each return visit the signs and symptoms of inflammation, scaling, and itching will be graded individually on a scale of from 1 to 5. A global evaluation of the status of the seborrheic dermatitis will be made using the same scale. The scale is defined as follows.

Symptomatology and global evaluation scale	
0	none
1	slight
2	mild
3	moderate
4	pronounced
5	severe

The percentage of scalp area affected will also be estimated.

The primary efficacy variable will be the response rate for the category 'Effectively Treated'. This is defined as scores at endpoint of 0 for scaling, inflammation, and status of seborrheic dermatitis, or, scores of 1 at endpoint if the baseline score was 3 or greater, for scaling, inflammation, and status of seborrheic dermatitis.

The response rate for the category 'Cleared' will also be

determined. This is defined as a score of 0 for scaling, inflammation, itching, and status of seborrheic dermatitis.

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Other response rates will be determined for overall improvement, for response in the individual signs and symptoms, and in the sumscores for scaling, itching, and inflammation.

8) Safety evaluations.

Adverse events will be recorded, with the severity and an assessment of the relationship to treatment. A subset of patients will have hematology and clinical chemistries performed.

Summary statements regarding the adequacy of the protocol:

- 1) The risks of the proposed study are acceptable in view of its objectives.
- 2) Adequate precautions are being taken.
- 3) The study objectives are clear and are based on a sound rationale.
- 4) The study protocol is adequate to provide data that will achieve the study objectives.
- 5) The informed consent form has not been reviewed.

Reviewer's comments: The efficacy parameters and the primary efficacy variable are the same as in the previous study # 3001.

Reviewer's evaluation:

- 1) The sponsor should provide the name of a principal investigator and the IRB for the study.
- 2) The sponsor should provide a rationale for the exclusion of women of childbearing potential who are not using adequate contraception.
- 3) The sponsor needs either to address plans for the study of patients younger than 18 years of age, or to request a waiver of such studies.
- 4) The ITT population should be defined as all patients who were randomized and dispensed the study medication. Also, for all patients, the last observation is carried forward (LOCF), regardless of the reason for discontinuation from the study.
- 5) It is preferable that the scoring scales for the individual clinical signs and for the investigator's global evaluation

provide a morphologic description of each category in the scale. In particular, the global evaluation is intended to provide a description of the patient's overall condition at the end of treatment, and the categories should be discrete, static, and sufficiently described so that inter-observer variability is minimized. (Single word descriptions such as slight, mild, etc., are not desirable.) The global evaluation is then dichotomized for analysis into two defined categories of 'Success' and 'Failure'. A Treatment Success would include only those patients in whom the condition has cleared or shows only minimal residual signs. The statistical comparison should be between the proportion of patients having a Treatment Success in the active group and in the vehicle group.

Dr. Friedlin was consulted on the validity of a possible change in the enrollment criteria during the study to include only patients with a baseline severity score of 3. She felt that the selection should not be arbitrary, with some of the patients having the same baseline score selected and some rejected. It was felt that a change in the enrollment criteria is acceptable, provided that the criterion was changed for all investigators at the same time to state that only those patients with a score of 3 or higher could now be enrolled.

Recommended comments to be conveyed to the sponsor: In regard to the questions posed in the correspondence of December 28, 2000, it is agreed that if statistical significance is reached for the primary efficacy analysis in the ITT population, then the requirements to demonstrate efficacy for Loprox shampoo will have been met. Additional comments on the analysis of the data are provided below. If effectiveness is demonstrated in the proposed study, the FDA concerns regarding the applicability of the European data to US populations will have been addressed.

Question #4 on the appropriate frequency of application to prevent recurrence of seborrheic dermatitis concerns a review issue, which will be addressed at the appropriate time.

In regard to Question #5, there is no objection to the proposed two week washout period preceding the treatment period.

We have the following additional comments:

- 1) The name of a principal investigator and the IRB for the study should be provided.

- 2) A rationale for the exclusion of women of childbearing potential who are not using adequate contraception should be provided.
- 3) Plans for the study of patients younger than 18 years of age should be addressed, or a waiver of such studies should be requested.
- 4) The ITT population should be defined as all patients who were randomized and dispensed the study medication. Also, for all patients, the last observation should be carried forward (LCCF), regardless of the reason for discontinuation from the study.
- 5) It is preferable that the scoring scales for the individual clinical signs and for the investigator's global evaluation provide a morphologic description of each category in the scale. In particular, the global evaluation is intended to provide a description of the patient's overall condition at the end of treatment, and the categories should be discrete, static, and sufficiently described so that inter-observer variability is minimized. (Single word descriptions such as slight, mild, etc., are not desirable.) The global evaluation is then dichotomized for analysis into two defined categories of 'Success' and 'Failure'. A Treatment Success would include only those patients in whom the condition has cleared or shows only minimal residual signs. The statistical comparison should be between the proportion of patients having a Treatment Success in the active group and in the vehicle group.
- 6) In regard to the validity of a possible change in the enrollment criteria during the study to include only patients with a baseline severity score of 3, it should be emphasized that the selection should not be arbitrary, with some of the patients having the same baseline score selected and some rejected. It is felt that a change in the enrollment criteria is acceptable, provided that the criterion is changed for all investigators at the same time to state that only those patients with a score of 3 or higher may now be enrolled.

COPY OF DFS VERSION

TEAM LEADER REVIEW OF AMENDMENT TO _____
AMENDMENT # 21

HFD-540 Trac No.: 017155
Doc ID: N (PN) 021

Correspondence date: 12/28/00
CDER Stamp date: 1/2/01

Review Date: February 16, 2001

SPONSOR: Medicis Pharmaceutical Corp, Scottsdale, AZ

DRUG: Loprox (ciclopirox) shampoo 1%

PHARMACOLOGIC CATEGORY: Antifungal

PROPOSED INDICATION: Seborrheic dermatitis of the scalp.

DOSAGE FORM AND ROUTE OF ADMINISTRATION: Shampoo

REASON FOR AMENDMENT: Submission of a Phase 3 protocol (45 day Special Protocol) in response to a non-approval letter.

RELATED NDA: NDA 21-159

These comments extend the primary medical review dated February 12, 2001.

Background:

The sponsor's original NDA 21-159 received a Non-Approval action on Sept 6, 2000. Sponsor was informed that there was a need to submit "an adequate and well-controlled study to demonstrate the effectiveness of Ciclopirox shampoo for the proposed labeling."

The sponsor has submitted Study 00-017 in response to the non-approval letter of Sept 6, 2000.

The sponsor's draft labeling of 8/16/99 contained in the original submission includes:

The conclusions of the original medical officer and team leader clinical reviews are summarized below:

Study 204

This study was unable to demonstrate that treatment of seborrheic dermatitis with Ciclopirox Shampoo either 1x, 2x, or 3x weekly for 4 weeks was more efficacious than vehicle treatment.

Study 3001

Segment A (treatment) – A three arm trial (vehicle twice weekly, drug product twice weekly, drug product once weekly and vehicle once weekly) which demonstrated that the use of Ciclopirox Shampoo 1x or 2x weekly for 4 weeks in patients with seborrheic dermatitis was more efficacious than treatment with vehicle.

Segment B — Patients who were determined to be “responders”¹ in segment A were randomized into this three arm trial (vehicle weekly, drug product weekly, drug product first week and vehicle second week). The study demonstrated that use of Ciclopirox Shampoo once a week or once every two weeks for 12 weeks was more effective than vehicle. The primary efficacy variable was the “relapse rate”, defined as a worsening of the global status score from the start of segment B by 2 or more points.

Team leader comments:

Submitted protocol 00-017 proposes to study the use of Ciclopirox shampoo used twice weekly for 4 weeks in the treatment of seborrheic dermatitis, similar to Segment A of study 3001. There is no proposal for a — segment. The design of a — trial does not appear to have been discussed with the division. The proposed study would only support labeling for the 4-week treatment phase.

Completed study 3001 demonstrated clinical success for both the twice weekly and once weekly treatment regimen. The sponsor proposes in this confirmatory study to use the drug product twice weekly. As once weekly treatment has been demonstrated to be efficacious, there appears to be no justification for using the drug product twice weekly.

The proposed labeling includes a claim for treatment of —. The sponsor does not appear to have done an analysis to specifically support this claim.

Clinical comment (Medical Officer’s review) regarding the enrollment criteria has not yet been discussed in a statistical review. This comment to the sponsor could be amended as follows:

¹ Responders defined as clear, or improvement to “1” if BL score was 3 or greater. The inclusion criteria included a score of “3” or higher for each of the categories of “status of seborrheic dermatitis, inflammation, and scaling”, therefore, all enrolled patients would be considered responders if they were able to achieve a score of 0 or 1.

Before we can commit to the validity of a possible change in the enrollment criteria during the study, please provide a discussion of how this would affect the statistical analysis of the data.

Comments to be conveyed to sponsor:

1. The design of proposed Study 00-017 plus completed Study 3001 (segment A) would support labeling for the treatment of seborrheic dermatitis (with the proviso that #2 below is addressed adequately).
2. The sponsor should provide adequate justification for the proposed use of the drug product twice weekly in Study 00-017. Results of Study 3001 (Segment A) indicate that both once and twice weekly were equally efficacious. Use of the product twice weekly appears to provide additional drug exposure without apparent clinical benefit. A rationale for using the product twice weekly instead of once weekly should be provided.
3. The sponsor's studies include "seborrheic dermatitis" in the inclusion criteria. Justification for labeling to include _____ should be provided.

Additional Comment:

Clinical comment (Medical Officer's review) regarding the enrollment criteria has not yet been discussed in a statistical review. This comment to the sponsor could be amended as follows:

Before we can commit to the validity of a possible change in the enrollment criteria during the study, please provide a discussion of how this would affect the statistical analysis of the data.


Susan J. Walker, M.D.
Clinical Team Leader

02/16/01

W DFS 02/16/01

HFD-540 Trac No: 017668
Doc ID: N-024 (MR)

Correspondence date: March 26, 2001
CDER Stamp date: March 28, 2001

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO _____
SERIAL # 24

DATE: May 7, 2001

SPONSOR: Medicis Pharmaceutical Corp.
Scottsdale, AZ

DRUG: Loprox (ciclopirox) shampoo 1%

PROPOSED INDICATION: Seborrheic dermatitis of the scalp.

REASON FOR AMENDMENT: Response to FDA comments on special
protocol # 00-017: request for Type A meeting/teleconference

DATE OF AMENDMENT: March 26, 2001

RELATED NDA: NDA 21-159

The present submission provides a response to each of the
comments in the FDA letter of February 16, 2001 on _____
Our letter concerned the review of special protocol # 00-017,
which was submitted by Medicis subsequent to the non-approvable
letter of September 6, 2000 on NDA 21-159 for Loprox shampoo.

The responses to the clinical portion of the letter are as
follows.

- 1) The name of a principal investigator and the IRB should be
provided.

Response: The investigator is Phoebe Rich, M.D., Portland,
OR, and the IRB is the Western IRB of Olympia, WA.

Evaluation: *The response is satisfactory.*

- 2) A rationale for the exclusion of women of childbearing
potential who are not using adequate contraception should be
provided.

Response: Ciclopirox is rated as Pregnancy Category B -
adequate and well-controlled clinical studies using
ciclopirox have not been performed in pregnant women.

Approved labeling for Loprox (ciclopirox) Gel 0.77% includes a statement under Precautions that Loprox Gel should only be used in pregnant women if the potential benefit justifies the potential risk to the fetus.

There is no evidence to suggest that a topical dosage form of ciclopirox in the dosage strength under study would present a significant risk to a developing fetus. However, the sponsor believes that it is prudent to exclude women of childbearing potential not using adequate contraception from clinical studies on Loprox shampoo.

It is unlikely that a sufficient number of pregnant women would be randomized to treatment with Loprox shampoo to allow Medicis to make definitive statements regarding safety in this population that would serve to change the current labeling precautions. Seborrheic dermatitis is not a life threatening disease that would justify a loosening of the risk/benefit precautions as they appear in current approved labeling for other ciclopirox topical products. In addition, it is not known if ciclopirox is excreted in human milk.

For these reasons the sponsor sees no justification in including women of child bearing potential (without adequate contraceptive use) in clinical trials on Loprox shampoo.

Evaluation: It is felt that the sponsor's rationale is adequate justification for the exclusion of women of childbearing potential who are not using adequate forms of contraception.

- 3) Plans for the study of children younger than 18 years of age should be addressed, or a waiver of such studies should be requested.

Response: Loprox Gel is currently indicated for patients 16 years or older. Inclusion criteria for Loprox shampoo will be broadened to include patients 16 years and older and the proposed labeling will reflect an indication for this population. However, seborrheic dermatitis of the scalp is not a common pediatric condition. The sponsor has already submitted a request for a waiver for pediatric studies using Loprox shampoo in NDA 21-159.

Evaluation: This response is felt to be satisfactory.

- 4) The ITT population should be defined as all patients who were randomized and dispensed the study treatment. Also, for all patients, the last observation should be carried forward (LOCF), regardless of the reason for discontinuation from the study.

Response: The ITT population for analysis purposes will be defined as all patients who were randomized and dispensed study treatment as requested by FDA.

The sponsor has additional comments on their approach to LOCF analysis:

Evaluation: The response in regard to the definition of the ITT population is satisfactory. The sponsor's approach to LOCF analysis needs to be addressed by our statistician.

- 5) Before we can commit to a possible two week washout period proceeding the treatment period, please provide a discussion of how this would simulate marketed conditions of use for your product.

Response: The sponsor will delete the two week washout period included in the current protocol. However, an exclusion criterion will be added that patients are to be excluded if a prescription or OTC medicated shampoo is used within the two weeks prior to study enrollment.

Evaluation: This response is felt to be satisfactory.

- 6) It is preferable that the scoring scales for the individual clinical signs and for the investigator's global evaluation provide a morphologic description of each category in the scale. In particular, the global evaluation is intended to provide a description of the patient's overall condition at the end of treatment, and the categories should be discrete, static, and sufficiently described so that inter-observer variability is minimized. (Single word descriptions such as slight, mild, etc., are not desirable). The global evaluation is then dichotomized for analysis into two defined categories of 'Success' and 'Failure'. A Treatment Success would include only those patients in whom the condition has cleared or shows only minimal residual signs. The statistical comparison should be between the proportion of patients having a Treatment Success in the active group and in the vehicle group.

Response: The study protocol (section 6.2.2) contains exact definitions of several dichotomized efficacy criteria, all dividing patients into 'successes' or 'failures'. In line with previous discussions with the FDA, the criterion 'effectively treated' was identified to be the primary efficacy criterion for the confirmatory analysis. The sponsor would like to know whether the FDA agrees that this criterion meets the FDA's request for successes (cleared or only minimal residual signs). It is indeed planned in the study protocol to compare the success rates between the active and the vehicle treatment group.

Evaluation: The response does not address the nature of the scoring scales for the individual signs and for the investigator's global evaluation. To repeat our comments in the letter of February 16, 2001, the scales should provide a morphologic description of each assessment category which is sufficient to minimize inter-observer variability. In contrast, each scale proposed in the protocol has only the following categories, with no further description given: none, slight, mild, moderate, pronounced, and severe.

In response to the sponsor's comment, the primary comparison should be of the proportion of patients that are cleared or have only minimal residual signs, whether this is termed 'Effectively Treated' or 'Treatment Success'.

- 7) Before we can commit to a possible change in the enrollment criteria during the study, please provide a discussion of how this will affect the statistical analysis of the data.

Response: FDA requested for Study 3001 that at least 70% of the patients should have scores of 3 (moderate) or worse at inclusion. The procedure outlined in section 5.1 of the study protocol has been adopted from Study 3001 to meet this request. No change of the enrollment criteria for Study 3001 due to this was required because the percentage of mild cases was very low. Should a change be needed in the current study, it would affect both treatment groups in the same way and thus not bias the treatment comparison; nevertheless in this case the sponsor suggests that an exploratory subgroup analysis be provided for the primary efficacy criterion (stratification: enrolled before/after this change of the enrollment criteria).

Evaluation: An evaluation by our statistician is needed.

- 8) The design of proposed Study 00-017 plus completed Study 3001 (segment A) would support labeling for the treatment of seborrheic dermatitis (with the proviso that #8 below is addressed adequately).

Response: No response is required.

- 9) Please provide adequate justification for the proposed use of the drug product twice weekly in Study 00-017. Results of Study 3001 (Segment A) indicate that both once and twice weekly were equally efficacious. Use of the product twice weekly appears to provide additional drug exposure without apparent clinical benefit. A rationale for using the product twice weekly instead of once weekly should be provided.

Response: Although both the once per week and twice per week treatment arms were significantly more efficacious than vehicle alone ($p=0.0015$ and $p=0.0001$) the response rate in the twice per week group was superior. Patients treated once per week had a response rate of 45.5% compared to 31.6% for the vehicle and patients in the twice per week group had a response rate of 58.5% compared to 31.6% for the vehicle.

Ciclopirox has a long history of use in the forms of creams, lotion, and gel with an excellent safety profile. Therefore, given the greater clinical response in the twice a week treated group and the low level of adverse events associated with ciclopirox use generally, the sponsor believes that twice a week treatment is the preferred regimen for Loprox shampoo 1%.

Evaluation: It is felt that the sponsor has provided adequate justification for the twice weekly use of Loprox shampoo.

- 10) Studies 3001 (A) and 00-017 include 'seborrheic dermatitis' in the inclusion criteria. Justification for labeling to include _____ should be provided.

Response: Medicis will remove the indication for _____ in the proposed labeling for Loprox shampoo 1%.

Evaluation: The sponsor's response is satisfactory.

Reviewer's overall evaluation: The response to the FDA comment #6 does not address the nature of the scoring scales for the individual signs and for the investigator's global evaluation, namely, the preference for morphologic description of the assessment categories. The response to comments #4 and #7 should be addressed by our statisticians.

The responses to the comments in our letter of February 16, 2001 are otherwise satisfactory.

Phyllis A. Huene, M.D.

Cc: Orig _____
HFD-540 Division files
HFD-540/DIVDIR/Wilkin
HFD-540/Clinical TL/Walker
HFD-540/MO/Huene
HFD-540/Friedlin
HFD-540/Lutwak

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

/s/

Phyllis Huene
5/7/01 11:03:25 AM
MEDICAL OFFICER

Susan Walker
5/10/01 04:28:34 PM
MEDICAL OFFICER
Concur with review

Jonathan Wilkin
5/25/01 12:47:08 PM
MEDICAL OFFICER

Comment to Sponsor: Sponsor's rationale for exclusion of women of childbearing potential could be considered for proposed labeling. Also, reviewer's "Evaluation #6" may be conveyed to Sponsor. Biostat should comment on #4 & #7.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Team Leader Addendum: NDA 21-159

JUL 11 2000

SPONSOR: Medicis Pharmaceutical Corp.

DRUG PRODUCT: Loprox (ciclopirox) shampoo 1%

CLINICAL INDICATION: _____ and seborrheic dermatitis of the scalp

Team Leader concurs with the medical reviewer's conclusion that this application not be approved. Clinical study #3001 is the only study sponsor has conducted in which a clinically and statistically significant treatment effect from the proposed drug product was demonstrated. This study is considered an adequate and well-controlled study to support the proposed indication, but does not, in and of itself, provide sufficient evidence for approval. An additional adequate and well-controlled study that demonstrates the proposed drug product provides a clinically and statistically significant treatment effect would be required for approval of this NDA.

The regulatory guidance entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" details the circumstances in which one clinical study would suffice for approval of an NDA: "generally...limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with a serious outcome and confirmation of the result in a second trial would be practically and ethically impossible." Because seborrheic dermatitis is not associated with mortality or serious morbidity, there would be no ethical constraints that preclude repetition of the trial to confirm the study #3001 results. Caveats regarding reliance on a single, multi-center study are discussed in the guidance:

It must be appreciated that even a strong result can represent an isolated or biased result...When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered

The following is a list of possible sources of bias or of possible lack of applicability of the study results to the U.S. population that preclude clinical study #3001 from being used, in and of itself, as sufficient evidence for approval:

- (1) Study #3001 was conducted in sites in several European nations (e.g., France, Germany, United Kingdom), but not in the United States. The sponsor has not provided a scientific rationale for why clinical efficacy results observed in Europe may be extrapolated to the United States. As was mentioned in the pre-NDA meeting, an application based solely on foreign clinical data meeting U.S. criteria for marketing approval should show that the data are applicable to the U.S. population and U.S. medical practice. Three pertinent differences that might be anticipated a priori to cause differences in treatment outcome across the different geographical regions include differences in the distribution of ethnic groups, possible differences in susceptibility of *Malassezia sp.* to ciclopirox (assuming that the clinical efficacy of ciclopirox shampoo is related to its microbicidal activity), and possible differences in

the type of hair care techniques and/or products used in different societies (which might impact the efficacy of a ciclopirox-containing shampoo).

- (2) Study #3001 had a two-week run-in phase during which subjects were instructed to use _____ shampoo at least twice weekly. After the run-in phase, subjects were randomly allocated to ciclopirox shampoo biw, ciclopirox shampoo qw, and vehicle shampoo biw. Patients were permitted to use _____ shampoo for additional shampoos during treatment as desired. The consequences on treatment efficacy of mandating use of _____ shampoo prior to and during treatment are unclear. If, for example, _____ shampoo potentiates the clinical efficacy of ciclopirox shampoo, then mandating _____ shampoo use would exaggerate any treatment effect observed in the clinical study. Since patients in general clinical practice would not engage in a run-in phase prior to using a prescription shampoo, and may not restrict the use of their non-medicated shampoos to _____, it may not be possible to extrapolate the clinical efficacy results observed in Study #3001 to general clinical practice.

Clinical studies #203 and #204 were Phase 2 concentration and frequency-ranging studies that were not adequately powered to demonstrate statistical superiority of the to-be-marketed formulation at the to-be-marketed dose frequency compared to placebo. Further, clinical study #203 collected retrospectively information about the primary efficacy variable considered by Agency to be most relevant for measuring clinical efficacy--the Investigator's Global Evaluation. The possibility of inaccuracy in assessing the primary efficacy variable retrospectively renders use of the results of this study suspect. For clinical study #204, the point estimate of the primary efficacy variable for the study arm of the to-be-marketed formulation at the to-be-marketed dose frequency is only marginally superior to that of the vehicle arm.

Clinical study #3003, designed to demonstrate non-inferiority of ciclopirox shampoo to ketoconazole shampoo, has the shortcoming that there was no placebo arm(s) in the study. At the pre-NDA meeting, sponsor was advised that a placebo arm is required in equivalence and non-inferiority trials to evaluate internal validity. In addition to this shortcoming, the shortcomings detailed for study #3001 are also applicable for study #3003.

/S/

7/06/00

Martin M. Okun, M.D., Ph.D.
Clinical Team Leader

cc:

Archival NDA

HFD-540

HFD-540/Dermatology Medical Reviewer/Huene

HFD-725/Biostatistics Team Leader/Al-Osh

HFD-725/Biostatistician/Freidlin

HFD-880/Biopharm/Bashaw/Adeboyele

HFD-540/Pharm/Nostrandt

/S/

7/11/00

HFD-540/Chemistry/Gautam-Basak
HFD-540/Project Manager/Lutwak

**APPEARS THIS WAY
ON ORIGINAL**

MEDICAL OFFICER'S REVIEW OF NDA 21-159
ORIGINAL SUBMISSION

March 27, 2000

SPONSOR: Medicis Pharmaceutical Corp.
Phoenix, AZ

MAY 21 2000

DRUG: Loprox (ciclopirox) shampoo 1%

CLINICAL INDICATION: _____ and seborrheic dermatitis
of the scalp

Proposed labeling indication statement: 'Loprox shampoo 1% (ciclopirox) is indicated for the topical treatment and _____; of seborrheic dermatitis of the scalp and _____ in adults.'

FORMULATION:

Ciclopirox 1%

Sodium chloride
Purified water

DOSAGE AND ADMINISTRATION: Applications of 5-10 ml - BIW for 4 weeks. For 1 _____

DATE OF SUBMISSION: August 31, 1999

RELATED SUBMISSIONS:

Application	Formulation	Indications
NDA 18-748 (approved 1982)	Loprox cream 0.77%	tinea pedis, tinea corporis, tinea cruris
NDA 19-824 (approved 1988)	Loprox lotion 0.77%	cutaneous candidiasis, tinea versicolor
NDA 20-519 (approved 1997)	Loprox gel 0.77%	tinea pedis, tinea corporis, tinea cruris, seborrheic dermatitis of the scalp
NDA 21-022 (approved 1999)	Loprox nail lacquer 8%	onychomycosis

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Pharmacologic class

Ciclopirox is a synthetic broad spectrum hydroxypyridone antifungal agent. The mode of action is an interference with a variety of metabolic processes in the fungal and bacterial cell.

Scientific rationale

The sponsor states that ciclopirox is indicated for the treatment of seborrheic dermatitis of the scalp and its minor form, _____ because of its antifungal activity against *Pityrosporum* spp., its antibacterial and anti-inflammatory effects, and its penetration properties.

The sponsor further states that *in vitro* studies have shown that ciclopirox inhibited the formation of inflammatory mediators in a cell culture model. *In vivo*, ciclopirox inhibited inflammation in a murine ear edema model, and a commercial ciclopirox cream was shown to suppress the delayed erythema response to UVB generated by a solar simulator in a human experimental model. In a study of the ability of ciclopirox to penetrate the stratum corneum and build up a reservoir in a short time, a study on excised pig skin showed significant antifungal activity in the stratum corneum after a contact time of five minutes.

Foreign marketing history

The shampoo formulation has not yet been marketed in a foreign country. The other ciclopirox formulations have been marketed since 1981 in more than 60 countries, and since 1983 in the US.

Pre-NDA meeting

A pre-NDA meeting on Loprox shampoo was held on April 29, 1999. The Agency's comments on the clinical issues and on the sponsor's questions for discussion, (as paraphrased in part) were as follows.

1. Regulatory status: All studies appear to have foreign data. The sponsor is referred to 21 CFR 312.120 and 314.106 with regard to acceptance of foreign data.
2. Indication: a) The proposed indication for seborrheic dermatitis is not location specific (see submitted Form FDA 1571, dated 3/5/1999, Item 7) Phase 3 trials conducted with this drug product for seborrheic dermatitis of the scalp only support an indication for seborrheic dermatitis of the scalp.

- The sponsor should explain any discrepancies in the results, such as why a higher disease relapse rate was present in the once per four day treatment arm (21.4%) versus the once per seven day treatment arm (14.4%) in Study 3001.
- It is recommended that the sponsor provide subset analyses for each of the following populations in their studies: those with dandruff, those with HIV infection, those with non-scalp seborrheic dermatitis, those of two different age groups, and those of African, Asian, Hispanic, or Caucasian descent.
- The primary efficacy variable for seborrheic dermatitis should incorporate both the physician's global score and the clinical signs and symptoms score.

Other clinical comments concerned submission in an electronic format, and submission of complete data. Other sponsor questions were deemed to be review issues, to be addressed in the review process.

Among the comments of the biostatistical reviewer were the following:

- For superiority studies 204 and 3001, approval will be contingent on the active drug being statistically significantly better than placebo relative to the primary efficacy variable at week 4. The primary efficacy population should be the ITT population, defined as all randomized patients who received the product. This definition was recommended by the Division in the Telecon with the Sponsor on December 4, 1996, and is documented on page 2 of the Memorandum of Teleconference. For the patients who lack any subsequent rating, the last observation should be carried forward, i.e., the baseline (visit 2) value should be used as the last value.
- According to the study report of Study 204, 183 subjects were randomized at visit 2. Therefore, all these 183 subjects should be included in the ITT population of Study 204. This is the ITT population that will be used in the FDA review. In order to ensure a timely review, the Sponsor is requested to provide a primary efficacy analysis for the ITT population including 183 subjects. All other ITT populations can also be used by the Sponsor, but will not be the Division's primary efficacy set.
- In Study 204, 17 subjects were enrolled in the run-in phase,

but were not randomized at visit 2. The Division needs to know the reasons for not randomizing those 17 subjects.

- Study 3003 is intended to demonstrate equivalence (non-inferiority) of Ciclopirox shampoo to Ketoconazole shampoo. According to Section 3.3.2. of the ICH E9 Document. The primary efficacy population for the equivalence and non-inferiority trials should be the Per Protocol (Valid Cases) population. A placebo arm is required in equivalence and non-inferiority trials to evaluate internal validity.

Additional comments were made concerning statistical methodology.

The comments of the Pharmacology/Toxicology reviewer were as follows.

- The studies submitted previously appear to address all pertinent areas usually addressed in an NDA, with the exception of adequate dermal carcinogenicity testing. Dr. Shuster said that treatment for this condition is not continuous, but may be episodic over most of a patient's life.

Since this product may be used on a chronic basis, albeit intermittently, a dermal carcinogenicity study of the shampoo formulation should be performed. . . It would be acceptable for the study to be submitted as an amendment to the NDA or to be completed and submitted in Phase 4. If it is difficult to limit the impurities as recommended by the reviewing chemist, then it is recommended that a 2 year study with complete toxicological evaluation be performed in order to aid in qualifying those impurities.

- The Sponsor is reminded of a previous request for a safety pharmacology study to investigate the potential cardiotoxicity of repeated doses of ciclopirox and to further define the mechanism of that toxicity.

Other Agency issues

An issue of potential cardiotoxicity with ciclopirox was addressed in previous clinical and toxicological reviews by Dr. Amy Nostrandt and Dr. Markham Luke.

Dr. Nostrandt noted that myocardial necrosis and hepatic toxicity were seen in rats and dogs at oral doses of 30 mg/kg and higher. The NOAEL in these studies was 10 mg/kg, indicating a steep dose-

response relationship. The sponsor was requested by fax of 3/16/99 to perform a safety study in animals which evaluates multiple doses and includes pharmacokinetic data to correlate toxicity such as EKG changes with serum drug concentrations. On 4/20/99 the sponsor submitted a compilation of data to support the cardiac safety and their position that the safety pharmacology study is not needed. In her review of this material, Dr. Nostrandt stated that based on the findings in animal studies and on comparison of clinical and nonclinical pharmacokinetics, it appears that there is a sufficient margin of safety demonstrated between human exposures to ciclopirox from this shampoo formulation and animal exposures at cardiotoxic doses. No additional nonclinical information regarding the cardiotoxic potential of ciclopirox was felt to be necessary at that time.

In his review of 8/10/99 on the sponsor's reply to the Agency request for information on the potential cardiotoxicity, Dr Luke states that the sponsor has provided epidemiological data on Loprox including post-marketing and study data, animal study data on cardiotoxicity, data from a human study on pharmacokinetics of ciclopirox olamine after single and repeated application of 1% ciclopirox olamine cream on skin, and pharmacokinetics of ciclopirox shampoo.

Since 1975, when ciclopirox cream was first marketed until March 30, 1999, a total of 803 adverse events were reported. Fifty patients experienced 53 cardiovascular adverse events, of which two cases involved arrhythmia. The first case occurred in Study 202, and was reviewed by the Division of Cardio-Renal Drugs, which stated that a single episode of non-sustained ventricular tachycardia that likely occurred at a time distant from the time of exposure is unlikely to be related to the drug. A second case of incomplete left bundle branch block in a 64 year old male was considered unrelated by the sponsor. In phase 1-4 studies 22,000 patients were treated, and according to the sponsor patients have been prescribed ciclopirox since 1988.