

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-159

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 2
Consult

NDA # 21-159

Date Completed: January 17, 2003

Reviewer: Albert T. Sheldon, Jr. Ph.D.

Sponsor (IND)/Applicant (NDA):
Medicis Pharmaceutical Corporation
4343 Camelback Road
Phoenix, Arizona 85018-2700

Chem/Ther. Type: Ciclopirox, antifungal

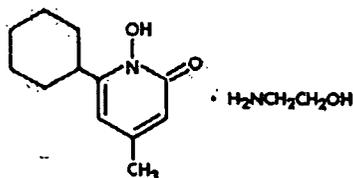
Submission Reviewed: August 29, 2002

Providing for: Treatment of seborrheic dermatitis of the scalp

Product Name(s):
Proprietary: Loprox
Non-proprietary/USAN: Ciclopirox
Compendia: NA
Code name/number: HOE 296b, hoe 296

Chemical name: 6-cyclohexyl-1-hydroxy-4-methyl-2(1 H)-pyridone, 2-aminoethanol salt

Structural formula:



Molecular formula: C₁₂H₁₇NO₂

Dosage form(s): Shampoo
Route(s) of administration: Topical

Pharmacological Category: antifungal agent

Dispensed: Rx X OTC

Initial Submission Dates

Received by CDER: August 31, 1999
Received by Reviewer: September 30, 1999
Review Completed: March 28, 2000

Supplements/Amendments:

Received by CDER: January 15, 2003
Received by Reviewer: January 15, 2003
Review Completed: January 16, 2003

Related Documents:

NDA 18-748 Loprox Cream (0.77%)
NDA 19-824 Loprox Lotion (0.77%)
NDA 20-519 Loprox Gel (0.77%)

Remarks:

The reader of this review should cross-reference Microbiological Review #1 completed by Dr. Joel Unowsky on March 28, 2000 and placed into DFS in January 2003. This review provides insight into some of the issues faced by the Microbiologist in the initial review. This review serves to address these concerns and to recommend the final product label as described below.

- The proposed microbiology section of the package insert states:

This section should be modified by deleting the information that states "
because this information is not relevant to the indication sought by the applicant. The indication sought is for the topical treatment of seborrheic dermatitis of the scalp of adults. The organism implicated in the pathogenesis of this condition is Malassezia. There are no other organisms implicated in the pathogenesis of this disease.

The justification for the deletion of the suggested material is an algorithm that clinical microbiologists use in the Division of Antiinfective Drug Products. This algorithm requires that only pathogens or information relevant to the indications under consideration is allowed in the Microbiology section of the package insert. In this case, only information on the susceptibility of Malassezia will be allowed because it is the only organisms implicated in the pathogenesis of seborrheic dermatitis.

Also, the last sentence states "

It is clear from the existing evidence that we can not state, with such certainty, that *Pityrosporum* spp causes seborrheic dermatitis. We should state " *Pityrosporum* spp. are implicated in the pathogenesis of seborrheic dermatitis of the scalp."

Finally, it is stated in the applicants EDR on page 01-098 that " *P. ovale* (oval cells) and *P. orbiculare* (round cells) are the saprophytic, yeast phase of the organisms, which is known as *Malassezia furfur* in its mycelial state. *M. furfur* is the causative agent of pityriasis versicolor and has also been associated with seborrheic dermatitis and dandruff formation." It is not clear to this reviewer whether the saprophytic yeast phase or the mycelial phase of the disease causes seborrheic dermatitis. The applicant seems to suggest, in the material quoted above, that it is the mycelial phase and perhaps the sentence should be re-written.

Thus, this reviewer suggests the following paragraph for the Microbiology section of the label:

"Ciclopirox is fungicidal, in vitro, against *Malassezia furfur* (*Pityrosporum* spp.), *P. ovale*, and *P. orbiculare* but the clinical significance of this information is unknown. *Malassezia furfur* is implicated in the pathogenesis of seborrheic dermatitis of the scalp."

- The package insert also provides information on the mechanism of action of Loprox. It states "Ciclopirox is a hydroxypyridone antifungal agent. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell."

This section should be moved to the Microbiology section of the package insert as we have done for other antifungal agents reviewed by the Microbiology staff.

Conclusions/Recommendations:

The microbiology section of the package insert should read as follows:

Microbiology

Activity in vitro: Ciclopirox is fungicidal, in vitro, against *Malassezia furfur* (*Pityrosporum* spp.), *P. ovale*, and *P. orbiculare*

NOTE: The clinical efficacy of this product for the treatment of fungal infections other than seborrhea dermatitis caused by *Malassezia furfur* has not been shown.

Albert T. Sheldon, Jr. Ph.D.
Microbiology Team Leader and Reviewer

IND/NDA No. 21-159
Loprox Shampoo 1.0%
Medicis Pharmaceutical Corporation
Microbiologist, HFD-520
File name: N21159_Loprox.doc

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SMicro/ATSheldon

DepDir/LGavrilovich

Cc: Original NDA #21-159
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ATSheldon
HFD-520/Micro
HFD-520/MO/
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/
HFD-520
HFD-502
HFD-635

¹ Mandell, Bennett, & Dolin. Principles and Practices of Infectious Diseases. 5th Edition, Volume 2, Chapter 257.

**APPEARS THIS WAY
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this page is the manifestation of the electronic signature.**

/s/

Albert Sheldon
1/17/03 03:37:24 PM
MICROBIOLOGIST

This is a Microbiological Review of NDA21159 submitted for
Loprox Shampoo for the treatment of seborrheic dermatitis

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21,159
Drug name Ciclopirox
Company name Medicis Pharmaceutical Corp.

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**Consultative Review to Department of Dermatological
and Dental products HFD-540
Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1**

NDA # 21-159

DATE COMPLETED:3/28/00

**APPLICANT(NDA):Medicis Pharmaceutical Corporation
4343 Camelback Roas
Phoenix arizona, 85018-2700**

CHEM/THER. TYPE: Ciclopirox, antifungal

SUBMISSION REVIEWED:Original NDA

**PROVIDING FOR:Treatment of seborrheic dermatitis of the scalp and it's
minor form of dandruff**

PRODUCT NAMES(S):

Proprietary: Loprox Shampoo

Non-Proprietary/USAN: Ciclopirox

CAS No.: 29342-05-0

Code Name : HOE 296B, Hoe 296

CHEMICAL NAME: See 1996 Usan (page 155)

MOLECULAR FORMULA: C₁₂H₁₇NO₂

MOL. WT. 207.27

DOSAGE FORM: Shampoo

STRENGTHS:1%

ROUTE OF ADMINISTRATION: Topical, to the scalp

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Drug name Ciclopirox
Company name Medicis Pharmaceutical Corp.

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PHARMACOLOGICAL CATEGORY: Antifungal (hydroxypyridone) agent

DISPENSED: ___ Rx ___

INITIAL SUBMISSION:

Received by CDER: August 31, 1999
Received by Reviewer: September 20, 1999
Review Completed: 3-28-00

RELATED DOCUMENTS:

APPROVED NDAs:

NDA 18-748, Loprox Cream (0.77%)
NDA 19-824, Loprox Lotion (0.77%)
NDA 20-519, Loprox Gel (0.77%)

PENDING NDA:

NDA 21-022, Loprox Nail Liquor (8%)

OPEN IND

REMARKS:

This review will be relatively brief and similar if not identical to previous microbiology reviews concerning Ciclopirox. Mr. Harold Silver of the Division of Antiinfective Drug products was the microbiology reviewer for NDA 20-519, Loprox Gel. That product included an indication for seborrheic dermatitis including the scalp. The applicant has referred to NDA submissions 20-519 and 18-748 concerning the vast majority of data regarding the anti-microbial activity and mechanism of action of Ciclopirox. In fact, no new information concerning the mechanism of action and very little concerning anti-microbial activity have been submitted for NDA 21,159 of a microbiology nature. The present reviewer agrees with the review of the mechanism of action of ciclopirox as submitted by Mr. Silver and recommends that the wording in the package insert concerning mechanism of action be identical with that for the Loprox Gel product. See letter of Jul 21, 1997 to HMR Attention J. Michael Nicholson, Ph.D. from Jonathan K. Wilkin, M.D. and review by Mr. H. Silver.

Drug name Ciclopirox

Company name Medicis Pharmaceutical Corp.

In his review Mr. Silver recommended that specific organisms not be mentioned in the package insert in association with treatment of Seborrhoeic dermatitis by Loprox Gel due to insufficient data and information. The present Reviewer agrees with the analysis of Mr. Silver as still being a fair analysis of the materials submitted for NDA 21,159 since no new Data that would change the earlier analysis has been submitted concerning the antimicrobial activity of ciclopirox. Efficacy versus relevant organisms was not demonstrated in the submitted clinical trials concerning the 1% shampoo formulation and was not shown by literature or internal company studies. Even though it is the responsibility of the applicant to submit relevant data in an organized manner, this reviewer conducted a literature review as well as having one conducted by professionals at our scientific library. In both cases, studies of the efficacy of ciclopirox versus recent clinical isolates and more important, recent isolates from the United States was not found.

The role of *Pityrosporum* sp yeasts in the pathophysiology of seborrhoeic dermatitis of the scalp and dandruff has been controversial for almost 100 years. Most of the other agents and treatment regimens for seborrhoeic dermatitis of the scalp and dandruff involve both anti-inflammatory and anti-fungal activities. *Pityrosporum* yeasts are the dominant organism in the normal flora of the scalp and comprise approximately 50% of the total number of organisms. *Pityrosporum* can comprise up to 88% of the scalp flora in dandruff and seborrhoeic dermatitis. However, the numbers of other organisms in the scalp flora especially *Propionibacterium acnes*, the second most numerous organism in the scalp flora decreases so the absolute numbers of *Pityrosporum* organisms might not increase. Thus it is unclear if the increase in numbers of *Pityrosporum* is real, coincidental and/or causal. When dandruff and seborrhoeic dermatitis improve the relative numbers of *Pityrosporum* yeasts decrease and, numbers of *P. acnes* increase but *Pityrosporum* species still remain in large numbers as the dominant species in the flora of the scalp. It will be the responsibility of the dermatology review team to define the role of *Pityrosporum* and/or inflammation in the pathophysiology of seborrhoeic dermatitis and dandruff of the scalp from a scientific and regulatory point of view.

The applicant has stated that he believes in the importance of *Pityrosporum* as a cause of seborrhoeic dermatitis and dandruff and the desirability of its subsequent elimination or reduction as being important in curing these conditions. The applicant desires to make certain statements in the microbiology section of the package insert which are relevant to *Pityrosporum* as an important factor in the pathophysiology of seborrhoeic dermatitis and dandruff. Therefore, my remarks concerning the microbiology review of this NDA will examine the microbiology issues assuming *Pityrosporum* species plays a major role in the pathophysiology of seborrhoeic dermatitis and dandruff of the scalp.

The FDA recognizes two lists of microorganisms in package product labeling. The first list includes organisms for which there is clinical

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and microbiological proof of cause of disease and against which the sponsor's drug has exhibited clinical efficacy. The second list includes organisms for which cause of disease and invitro efficacy has been demonstrated but clinical efficacy has not been proven.

Concerning the first list, there is no clinical proof of clinical efficacy concerning killing or inhibition of *Pityrosporum sp* in clinical studies using the Loprox 1% shampoo. As stated by the applicant on p. 10 of volume 28, "The clinical microbiological results concerning the assessment of *P. ovale* from skin samples of patients enrolled in clinical trials 204 and 203 can not be used because few microbiological results are available from either study."

Concerning the second list, specific requirements are described in the NDA holders letter dated 1/26/93. These specific requirements include the demonstration of invitro activity against 100 clinical isolates originating from a broad geographic distribution. It is necessary that the majority of strains be isolated in the United States. The applicant did not meet these requirements.

The applicant refers to two earlier original NDAs, Loprox cream 1% (NDA 18-748) and Gel 0.77% (20-519) for microbiological data and states that, "the major studies which demonstrate the mechanism of action and microbiological activity of ciclopirox and ciclopirox olamine (Loprox) have been submitted to the other Loprox INDs and NDAs sponsored by Hoechst-Roussel Pharmaceutical, Inc. (HMRPI), a subsidiary of Hoechst AG, the predecessor company to Hoechst Marion Rouselle Inc. (HMR)." It is of interest that the Loprox Gel is also indicated for the treatment of seborrheic dermatitis. In his recommendation, the microbiology reviewer for that NDA, Harold Silver recommended that *P. ovale* not be included in the labeling for the NDA 20,159 due to, "insufficient information and data". In fact, no organisms were included in the recommended draft package insert for Loprox Gel concerning the indication for Seborrheic dermatitis including seborrheic dermatitis of the scalp. (See letter of Jul 21, 1997 to Dr. J. Michael Nicholas, Ph.D. of HMR, from Dr. Jonathan K. Wilkin, M.D.) This reviewer found only the study of Markus relevant to the activity of Loprox shampoo versus *P. ovale*-no studies with *P. obiculare* were included. The studies of Markus were conducted with only 5 strains,

three of which are from a culture collection and two of which are of unknown origin. Thus these five strains are far short of the needed 100 strains of diverse geographical origin with the majority of isolates to be from the United States.

Specific questions and comments:

The FDA medical officer assigned to this NDA was concerned, "that the strains of *P. Ovale* in the European studies might differ from those in the US"

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It is not possible to answer the concerns of the medical officer with available data because:

1. Strains of *P. ovale* were isolated with low frequency during the clinical studies submitted and were not examined for susceptibilities to ciclopirox or other antifungals.
2. Tests of susceptibility to ciclopirox presented by the applicant were unpublished and were conducted on strains that by now are 20 or more years old.
3. In all cases it appeared that strains tested for susceptibility to ciclopirox by or referred to by the applicant were old and from Europe-US isolates have not been examined.
4. Thus, relevant and recent clinical isolates have not been examined.

A Pre-NDA meeting was held with the applicant on April 29, 1999. At that meeting there were several clinical microbiology comments and questions regarding data and information to be included in the NDA package. There follows a discussion of the questions, answers and comments of the microbiology reviewer. The applicant addressed these questions and comments in volume 28, p. 10.

1. Concerning the semi-quantitation of *P. ovale*, categories are defined as no entry, absent, very few, some, many and abundant upon microscopic examination. The sponsor has not associated any numbers with these categories. The majority of patients have no entry or absent. It is difficult to understand how such a large number of patients can have absent pathogens since the literature references provided, almost 100% of adults have *Pityrosporum* sp in their scalp which appears to even increase in dandruff and seborrheic dermatitis. Therefore, the applicant's methods and any conclusions drawn from them are invalid and can not provide supportive evidence for efficacy of Loprox 1% Shampoo.
2. Insufficient data is provided to evaluate the activity of Loprox shampoo against *P. ovale* and no data is presented for the activity versus *P. obiculare*.
3. Minimal data is presented characterizing the activity of ciclopirox against bacteria and other flora that normally resides in the scalp region. The activity provided by the applicant is unpublished, conducted 20 years ago, studies old isolates and does not include isolates from the ciclopirox shampoo clinical trials or recent US isolates.
4. Mechanism of action information was included in previous submissions and is repeated in summary in this application. Studies were not conducted specifically using *Pytirosporum* sp but are a compilation of results from studies in several genera and species.
5. Concerning the development of resistance, experimental studies have been not conducted by the applicant nor appeared in the scientific literature. The application said that resistance is not reported in the literature for ciclopirox in contrast to ketoconazole. The reviewer feels that this is an unfair comparison as ketoconazole has

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6. been available commercially for many years and there are over 10,000 articles referenced in medline while only a few hundred appear for ciclopirox. The Ketoconazole package insert includes the statement that resistance has not been observed and the applicant does not provide specific reference to resistance development to Ketoconazole. The fact that ciclopirox acts by a new mechanism of action indicates a probable lack of cross resistance to other antibiotics but does not a priori mean that resistance will not develop to ciclopirox. There are many classes of antibiotics that had new and unique mechanisms of action but resistance did develop to them. Sometimes it occurs sooner and sometimes it occurs later but resistance has developed to all commercially available classes of antibiotics.

CONCLUSIONS and/or RECOMMENDATIONS:

From the clinical microbiology point of view the submission is not acceptable because the applicant has failed to provide sufficient information and data to evaluate the invitro and/or clinical microbiology effectiveness of ciclopirox 1% shampoo:

1. The applicant has not proven efficacy in their clinical studies versus causative organisms as mentioned in their

2. —

3. Has not studied the activity of ciclopirox shampoo against recent United States clinical isolates.

Since the role of *Pytirosporium* yeasts in the pathophysiology of seborrheic dermatitis and dandruff has been controversial for over 100 years, it will be the responsibility of the dermatology review team to evaluate the acceptability or non-acceptability of the NDA.

/S/

4/18/00

Joel Unowsky, Ph.D.
Microbiology Review Officer
HFD-520

NDA 21,159
Drug name Ciclopirox
Company name Medicis Pharmaceutical Corp.

Concurrence only;
SMicro/ASheldon

BD and Final Initialed 4/18/00 CASS

TS 4/18/00

DepDir/LGavrilovich

120 4/18/00

cc: Orig. NDA #21,159
HFD-520/Micro/JUnowsky
HFD-540/CSO/VLitwak-for distribution
HFD-540/DeptDir/JWilkin

**APPEARS THIS WAY
ON ORIGINAL**