DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR - 7 2000

**TRANSMITTED VIA FACSIMILE**

Mark D. Reeth
Assistant General Counsel
MEDICIS Pharmaceutical Corp.
8125 North Hayden Road
Scottsdale, AZ 85258

Re: NDA 18-748
Loprox (ciclopirox) 0.77% Cream and Lotion
MACMIS ID# 8584

Dear Mr. Reeth:

As part of our routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials for Loprox (ciclopirox) 0.77% cream and lotion by Medicis Pharmaceutical Corp. (Medicis) that violate the Federal Food, Drug and Cosmetic Act and its implementing regulations. Reference is made to visual aids LPX37899 and LPX35998, a product monograph LPX36999, and a post-it note pad.

**Unapproved Uses**

Promotional material for a prescription drug is false, lacking in fair balance, or otherwise misleading if it contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. Throughout your promotional materials you promote Loprox as a treatment against gram negative and gram positive bacteria, a sporicidal with reliable treatment for dormant spores, and an anti-inflammatory agent with reliable treatment for inflamed mycoses without the additional risks of corticosteroid side effects. These uses for Loprox are not supported by substantial evidence. Furthermore, your materials make superiority claims over other anifungals. For example, In your product monograph LPX36999, you state, *"Unlike other antifungals, ciclopirox provides additional therapeutic advantages. It has been shown to have fungistatic, fungicidal, sporicidal, and anti-inflammatory properties and to be active against gram-negative and gram-positive bacteria."* As stated above, you have not demonstrated that Loprox is effective or superior to other agents for these uses. Therefore, these presentations promote Loprox for unapproved uses.

**Unsubstantiated Superiority Claims**

***Unique Mode of Action***

In addition, you make claims suggesting that Loprox is superior to other antifungals because it is the only hydroxypyridone antifungal that provides a unique mode of action that makes it effective against a wide range of cutaneous mycoses. For example, in your product monograph, you state, *"Ciclopirox exhibits a unique and complex mode of action. It is a substituted hydroxypyridone with a structure different from other antifungal preparations."* Furthermore, you state, *"This mode of action makes ciclopirox an appropriate choice for topical treatment alone, or as concomitant treatment when a topical product is indicated in combination with an oral antifungal drug."* These claims are unsubstantiated and therefore false and misleading.

***Penetration and Dose-Response Curve***

You make claims suggesting that Loprox is superior to other antifungals based upon studies regarding the penetrability of the drug and its steep dose-response curve. For example, in a reference to Loprox's dose-response curve and growth inhibiting capacity at low concentrations, you state in your product monograph, *"These features combined with its high penetrability through dry horny tissue suggest that consistent use of ciclopirox results in better pathogen elimination than would occur with antimycotics with flat dose-response curves (partial activity) such as miconazole."* These claims are misleading because they suggest that the drug is more effective than another drug when this has not been demonstrated by substantial evidence.

**Lack of Fair Balance**

In general, promotional materials are lacking in fair balance, or otherwise misleading if they fail to present the information relating to the contraindications, warnings, precautions, and side effects associated with the use of a drug in a manner reasonably comparable with the presentation of information relating to the effectiveness of the drug. In your promotional materials you prominently promote the efficacy of Loprox using colorful graphics, bar charts and clearly defined headings. In contrast, your visual aid LPX35998 does not disclose *any* risk information associated with the drug. In your product monograph LPX36999, you allot 14 pages to discuss the attributes of Loprox. In contrast, only one paragraph of the 14 pages is dedicated to the risk information regarding the drug. Similarly, your visual aid LPX37899 contains several pages presenting Loprox's efficacy, however, presents the risk information in the last paragraph on the last page of the visual aid. These presentations are lacking in fair balance with respect to both content and prominence of risk information.

Furthermore, your post-it note pad presents the claim "Loprox redefines broad-spectrum". However, there is no risk information presented to balance this claim. Therefore, the note pad lacks fair balance. Furthermore, this piece is in violation of the Act because it was not disseminated with the approved product labeling.

In addition, in your visual aid LPX37899, you claim that clinical studies show a 0.5% incidence of adverse reactions to Loprox. In the product label, another study is described that shows a higher incidence of adverse reactions. By choosing to present the lower number, Medicis is selectively presenting the most favorable result, and therefore, suggesting that Loprox is safer than has been demonstrated.

**Failure to Submit on Form FDA 2253**

You are in violation of the postmarketing reporting requirements because one of your promotional pieces, i.e. LPX37899, was not submitted to the FDA on Form FDA 2253 at the time of initial dissemination.

**Action Requested**

You should immediately cease distribution of these promotional materials and all other promotional materials for Loprox that contain the same or similar claims or presentations commented on in this letter. You should submit a written response to us, on or before March 21, 2000, describing your intent and plans to comply with the above. In your letter to us, you should include a list of all promotional materials that were discontinued, and the discontinuation dates.

You should direct your response to me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official. In all correspondence regarding this particular submission, please refer to MACMIS ID# 7644 in addition to the NDA number.

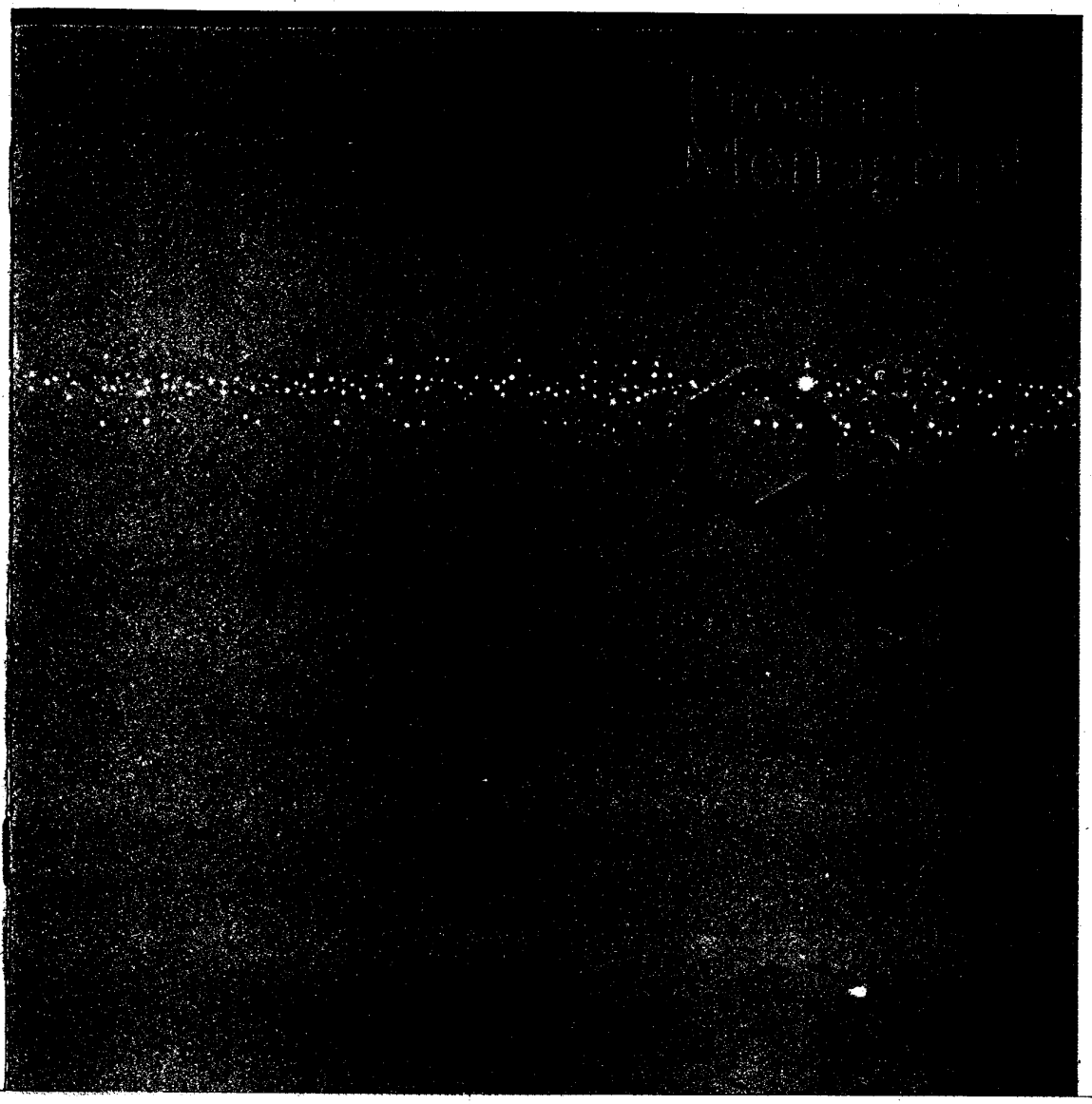
Sincerely,

/S/

Cheryl Y. Roberts
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

LOPROX®
(ciclopirox) Cream or Lotion

4343 East Camelback Road
Phoenix, AZ 85018
Phone: (800) 550-5115



LOPROX®
(ciclopirox) Cream or Lotion

# Table of Contents

Fungal infections, once considered relatively benign, are recognized by the medical community as a serious public health concern. In some cases, treatment is unsuccessful due to poor patient treatment compliance, continued exposure to infection, or drug-resistant strains of fungi. Additionally, some infections are now known to be life-threatening in immunocompromised patients, including those with HIV.

A recent (1997) national survey of dermatologists regarding topical fungal infections suggests that tinea pedis accounts for 21% of the infections they treat, tinea versicolor for 15%, tinea cruris and tinea corporis each 9%, cutaneous candidiasis 8%, tinea capitis 4%, and onychomycosis 18%.[1]

Historically, topical treatments for fungal infections were limited to imidazole compounds, of which a wide range of products are available. Gradually, additional options including allylamine and butalymine compounds were introduced. While these preparations have shown varying degrees of usefulness as treatments for specific fungal infections, each is limited in its scope of therapeutic action.

Ciclopirox, the only hydroxypyridone antifungal agent, has a unique mechanism of action that results in a broad range of clinical effectiveness. Additionally, with proven anti-inflammatory effects and a solid safety profile, ciclopirox offers the physician a treatment modality with a combination of properties not generally available in other topical antifungals.

## Indications and Description

LOPROX® (ciclopirox) Cream and Lotion are for topical use.

Each gram of LOPROX Cream contains 7.70 mg of ciclopirox, as ciclopirox olamine, in a water miscible vanishing cream base consisting of purified water USP, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative.

LOPROX contains the synthetic, broad-spectrum antifungal agent ciclopirox, as ciclopirox olamine. The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt. The CAS Registry Number is 41621-49-2.

LOPROX Lotion 0.77% contains the same ingredients as the Cream formulation, with the exception of the cocamide DEA, in a water miscible lotion base.

Ciclopirox, a hydroxypyridone, broad-spectrum antifungal agent, is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, tinea corporis, tinea versicolor, and cutaneous candidiasis.[2] Unlike other antifungals, ciclopirox provides additional therapeutic advantages. It has been shown to have fungistatic, fungicidal, sporicidal, and anti-inflammatory properties and to be active against gram-negative and gram-positive bacteria. Specifically, ciclopirox inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur*; it exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida albicans.*[2,3]

## Chemistry

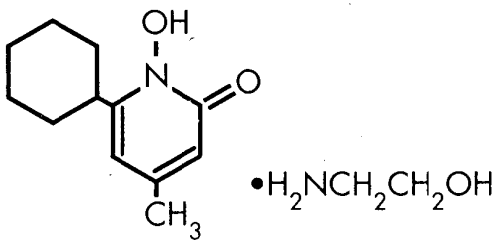
Structurally, ciclopirox is unrelated to the common imidazole derivatives or other antifungals. (Figure 1) The synthetic, broad-spectrum antifungal agent ciclopirox olamine has the chemical name 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt. The CAS Registry Number is 41621-49-2.

Ciclopirox is further differentiated from other antifungal agents by its unique mechanism of action that affects the cytoplasmic membrane but does not affect sterol biosynthesis.[3] This mode of action makes ciclopirox an appropriate choice for topical treatment alone, or as concomitant treatment when a topical product is indicated in combination with an oral antifungal drug. Ciclopirox is associated with an exceptional safety profile and a very low incidence of side effects.[2]



**Figure 1**

Chemical structure of ciclopirox olamine



# Mechanism of Action

Ciclopirox exhibits a unique and complex mode of action. It is a substituted hydroxypyridone with a structure different from other antifungal preparations. Unlike most antifungal agents, it does not affect sterol biosynthesis.[3] Ciclopirox primarily affects iron-dependent enzyme systems (e.g., cytochromes, catalase, peroxidase). It impairs the activity of mitochondrial heamoproteins by binding with iron, thus killing the cell organism. Ciclopirox affects the cytoplasmic membrane where it appears to impair active transport mechanisms, cell respiratory processes, and membrane integrity. Ciclopirox also negatively influences the macromolecular synthesis of nucleic acids and proteins. (Figure 2)

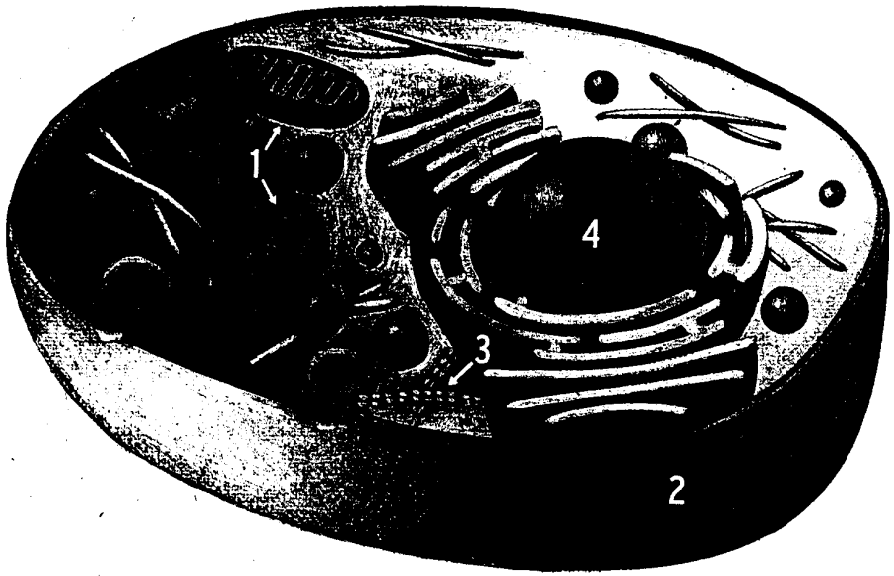



**Figure 2**

Mode of action, ciclopirox

1. Mitochondria
2. Cytoplasmic membrane
3. Ribosomes
4. Nucleus

**Table 1**

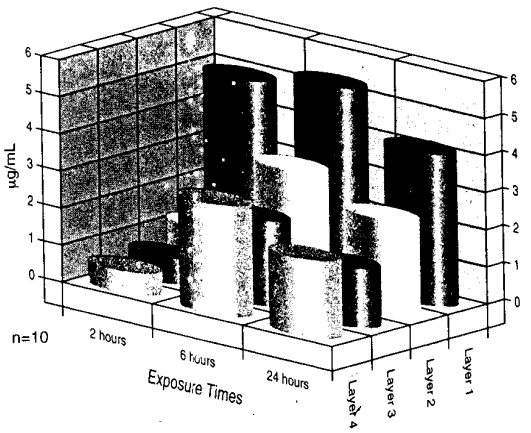
Fungicidal activity of antifungal compounds in pig skin model against *T. mentagrophytes* (1 hour of exposure)[5]

| | % Fungicidal Action |
|---|---|
| Ciclopirox | 98% |
| Oxiconazole | 73% |
| Naftifine | 64% |



**Table 2**

Concentration of ciclopirox (µg/mL) in four layers of human stratum corneum after different exposure times[4]




## Penetration

Bioavailability in the horny layer is an important first element of mycoses treatment, because dermatophytes and *Candida* species show a strong affinity for the stratum corneum. *In vivo* penetration of ciclopirox throughout the stratum corneum has been demonstrated within two hours. At only six hours, measurable levels of ciclopirox approached minimum inhibitory levels for sensitive organisms.[4] Ciclopirox (93%) is associated with superior *in vitro* penetration throughout the base layer of the stratum corneum compared to econazole (50%), clotrimazole (39%), and miconazole (28%).[5]

High levels of ciclopirox penetration were also demonstrated in two studies. First, *in vitro* testing showed that ciclopirox had consistently low minimum inhibitory concentration values (MICs) against a broad range of dermatophytes and yeasts. For most dermatophytes and yeasts the MIC falls within the range of 0.9 to 3.9 µg/mL.[3,5] Ciclopirox also exhibited faster penetration and greater inhibitory or fungicidal activity compared to azole compounds and other antimycotic formulations. In porcine skin treated with antifungal cream formulations, ciclopirox had the greatest fungicidal activity against *Trichophyton mentagrophytes* after one hour of exposure, compared to naftifine and oxiconazole.[5] (Table 1)

In the second study, in human volunteers (n=10), ciclopirox reached high concentrations sufficient to inhibit and kill pathogenic fungi in four different levels of human stratum corneum. The highest concentration was found in the layer close to the stratum lucidum, where the fungi approach living tissue. These findings are particularly relevant since they correlate with the excellent clinical efficacy associated with ciclopirox therapy.[4] (Table 2)

## Dose-Response Curve

Ciclopirox has a steep dose-response curve and shows total growth inhibiting capacity at low concentrations (3.9µg/mL – 15.6µg/mL). These features combined with its high penetrability through dry horny tissue suggest that consistent use of ciclopirox results in better pathogen elimination than would occur with antimycotics with flat dose-response curves (partial activity) such as miconazole. (Table 3) Poor compliance while using ciclopirox would therefore become quickly evident and steps to correct the situation could be promptly initiated. By comparison, underdosage of antimycotics with flat dose-response curves is more likely to remain unrecognized.[6]

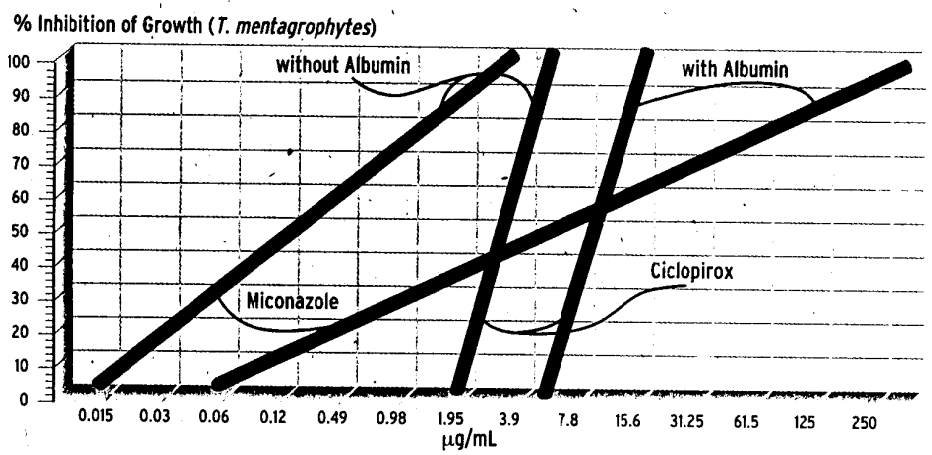



**Table 3**

Dose-response curve: ciclopirox compared to miconazole with and without 4% bovine albumin in agar medium

# Clinical Efficacy and Safety

Ciclopirox provides fast-acting fungicidal activity in a broad range of mycoses. Clinical studies have shown ciclopirox to be well-tolerated and effective at inhibiting the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur*. It exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida albicans*.[2]

**Table 4**

Comparative clinical improvement after 1 week of treatment

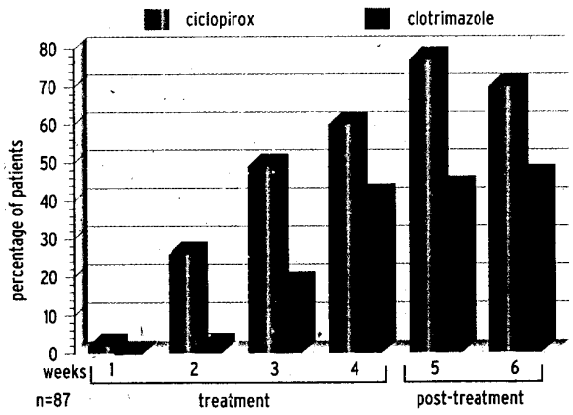
| | Ciclopirox | Imidazole Comparator |
|---|---|---|
| Tinea pedis | 95% | 76% |
| Tinea versicolor | 95% | 79% |
| Cutaneous candidiasis | 87% | 73% |
| Tinea corporis/ Tinea cruris | 97% | 94% |

## Ciclopirox Versus its Vehicle Cream Base

In several well-controlled, multi-centered, six-week studies, clinical improvement rates and mycological cure rates for subjects treated with ciclopirox showed statistically significantly greater improvement compared with those treated with its vehicle cream base for the following conditions: tinea pedis, cutaneous candidiasis, tinea corporis, and tinea cruris. In an additional four-week, well-controlled, multi-centered study, ciclopirox was associated with significantly greater rates of clinical improvement and microbiological cure than its vehicle, in the treatment of tinea versicolor.[7,8,9,10]

**Table 5**

Percentage of tinea pedis patients treated with ciclopirox or clotrimazole exhibiting combined clinical and mycological cures[7]




## Ciclopirox Versus Imidazole at One Week

In all comparative studies, clinical improvement after one week of treatment with ciclopirox was superior to that seen with an imidazole comparator (clotrimazole).[7,8,9,10] (Table 4)

## Tinea Pedis

In a blinded, controlled, multi-centered study of ciclopirox versus clotrimazole in the treatment of tinea pedis, 87 patients were evaluated at weeks one through four while receiving antifungal treatment and then again at weeks five and six during which time they were drug-free. Significantly more ($p<0.05$) patients who were treated with ciclopirox than those treated with clotrimazole achieved clinical and mycological cures. Both ciclopirox and clotrimazole were well-tolerated.[7] (Table 5)

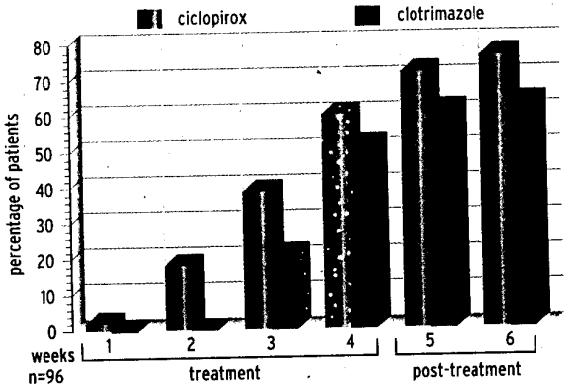
## Cutaneous Candidiasis

The candicidal activity of ciclopirox compared to other antimycotic agents was evaluated in a porcine skin model by Aly, et al. Ciclopirox demonstrated the most fungicidal activity, followed by tioconazole, oxiconazole, miconazole, econazole, clotrimazole and naftifine.[11]

Bagatell, et al. report the results of a six-week, multi-centered study (n=96) designed to evaluate the efficacy of ciclopirox 1% cream versus clotrimazole 1% cream in the treatment of cutaneous candidiasis. Following one, two and three weeks of treatment, significantly better clinical responses were recorded in the 48 patients who were treated with ciclopirox than those who were treated with clotrimazole. Mycological responses were similar in each group at two and four weeks post-treatment. (Table 6) No side effects were reported in either treatment group.[8]

**Table 6**

Percentage of cutaneous candidiasis patients treated with ciclopirox or clotrimazole exhibiting combined clinical and mycological cure[8]




## Tinea Versicolor

Efficacy and safety of ciclopirox olamine cream 1% versus clotrimazole cream 1% was assessed in a randomized, double-blind, parallel study (n=113) conducted at five medical centers.[9] After two weeks, all 60 patients who received ciclopirox improved and 77% had both a clinical cure and negative findings on the KOH smear. Of the 53 patients who received clotrimazole, although 91% improved, only 45% had both a clinical cure and negative results on the KOH smear. (Table 7)

At two weeks post-treatment, significantly more ($p \leq 0.05$) of those treated with ciclopirox remained clinically cured and the proportion of patients with a combined response (clinical and mycological cure) continued to be greater in the ciclopirox-treated group (86%) compared with the clotrimazole-treated group (73%). (Table 7) No side effects were observed in either treatment group.

**Table 7**

Percentage of tinea versicolor patients treated with ciclopirox or clotrimazole exhibiting combined clinical and mycological cure[9]

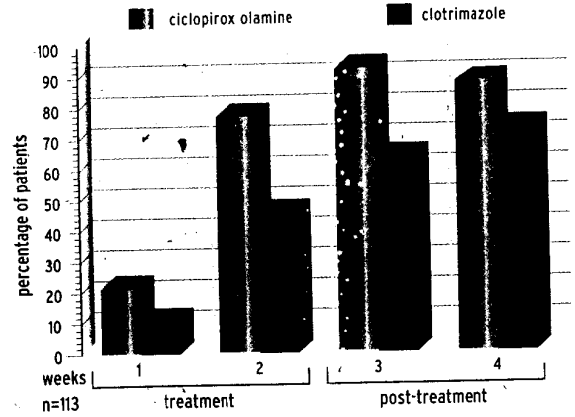


**Table 8**

Percentage of tinea corporis/tinea cruris patients treated with ciclopirox or clotrimazole exhibiting combined clinical and mycological cure[10]

| End of Week | ciclopirox olamine | clotrimazole |
|---|---|---|
| 1 | 3% | 2% |
| 2 | 23% | 18% |
| 3 | 46% | 38% |
| 4 | 64% | 69% |
| Post-Treatment Week | | |
| 5 or 6 | 63% | 71% |

n=90

**Table 9**

*In vitro* activity of ciclopirox, clotrimazole and miconazole against gram-positive and gram-negative bacteria and mycoplasma

| Organisms | MIC Range (mg/mL) | | |
|---|---|---|---|
| **Gram-Positive Strains** | | | |
| | Ciclopirox | Clotrimazole | Miconazole |
| *Staphylococcus aureus* | 7.8-15.6 | 0.98-3.9 | 0.49-1.95 |
| *Streptococcus pyogenes* | 3.9-15.6 | 1.95-15.6 | 0.49-15.6 |
| *Streptococcus* species (5 strains) | 0.196-7.8 | 0.20-1.6 | 0.005-1.95 |
| *Corynebacterium diphtheriae* | 31.5 | 3.9 | 31.5 |
| *Corynebacterium pyogenes* | 31.5 | 62.5 | 125 |
| *Listeria monocytogenes* (5 strains) | 15.6 | 0.98 | 0.24 |
| *Erysipelothrix insidiosa* | 7.8 | 0.391 | 0.05 |
| *Bacillus* species (5 strains) | 3.9-7.8 | 0.49-1.95 | 0.24-1.95 |
| *Sarcina lutea* | 3.9 | 0.049 | 0.025 |
| **Gram-Negative Strains** | | | |
| *Pasteurella septica* | 0.8 | >125 | >125 |
| *Pasteurella pseudotuberculosis* | 7.8 | >125 | >125 |
| *Salmonella* species (6 strains) | 15.6-31.5 | >125 | >125 |
| *Shigella flexneri* | 7.8 | >125 | >125 |
| *Escherichia coli* | 7.8-31.5 | >125 | >125 |
| *Enterobacter cloacae* | 31.5 | >125 | >125 |
| *Enterobacter aerogenes* | 125 | >125 | >125 |
| *Paracolobactrum* species (3 strains) | 7.8-15.6 | >125 | >125 |
| *Klebsiella pneumoniae* | 7.8 | >125 | >125 |
| *Proteus mirabilis* | 31.5-125 | >125 | >125 |
| *Pseudomonas aeruginosa* | 31.5-125 | >125 | >125 |
| *Mycoplasma* species (6 strains) | 7.8-31.5 | 62.5-125 | 62.5-125 |



## Tinea Corporis/Tinea Cruris

A six-week, controlled, blinded, multi-centered study (n=90) assessed the efficacy of ciclopirox cream 1%, its vehicle cream base, and clotrimazole cream 1% in the treatment of tinea corporis and tinea cruris. Clinical and mycological evaluations were made pre-treatment, at the end of each of the four treatment weeks, and at the end of each of the two drug-free post-treatment weeks. Ciclopirox achieved demonstrable improvements after the first week of therapy and complete clinical and mycological clearing in two-thirds (64%) of the patients at the end of the treatment period. These results remained consistent throughout the two-week post-treatment period. Ciclopirox was associated with significantly better results than the vehicle, while clotrimazole results were equivalent to those of ciclopirox. All treatments were well-tolerated.[10] (Table 8)

## Efficacy in Gram-Negative and Gram-Positive Organisms

Ciclopirox has shown *in vitro* activity against a variety of gram-positive and gram-negative bacteria.[3] Ciclopirox is associated with a higher rate of antibacterial activity compared to other antimycotic drugs, especially as it relates to gram-negative bacteria. Comparative *in vitro* studies evaluating the antibacterial activity of ciclopirox versus the imidazoles clotrimazole, miconazole, and ketoconazole, demonstrated a somewhat higher range of MIC values for ciclopirox than for clotrimazole and miconazole for gram-positive bacteria, but substantially lower values for gram-negative bacteria.[3] (Table 9) Lower MIC values were associated with ciclopirox versus ketoconazole for all gram-positive and gram-negative strains tested.[12]

**Table 10**

Fungicidal activity of antifungal compounds in human skin against *T. mentagrophytes*[11]

| | % Fungicidal Action |
|---|---|
| Ciclopirox cream 1% | 99 |
| Ciclopirox lotion 1% | 94 |
| Oxiconazole cream 1% | 62 |
| Naftifine cream 1% | 68 |

## Fungicidal and Sporacidal Efficacy

In an *in vivo* comparitive study using human skin samples, Aly, et al. demonstrated ciclopirox to have greater fungicidal activity against *T. mentagrophytes* than either naftifine or oxiconazole.[11] (Table 10)

*In vitro*, ciclopirox has demonstrated fungicidal and sporacidal activity in proliferating and non-proliferating conditions. At concentrations as low as 2.5 µg/mL, ciclopirox kills over 70% of fungal spores by day six of treatment with some activity seen within 24 hours. At increased concentrations (40 µg/mL), the kill rate exceeds 90% of non-proliferating fungal phases in the six day treatment time. (Tables 11 and 12)[12] This exceptional non-proliferating fungal phase activity may relate to the low relapse rate reported during the post-treatment weeks of ciclopirox clinical trials.[7,8,9,10]

**Table 11**

Fungicidal activity of ciclopirox (proliferating conditions)

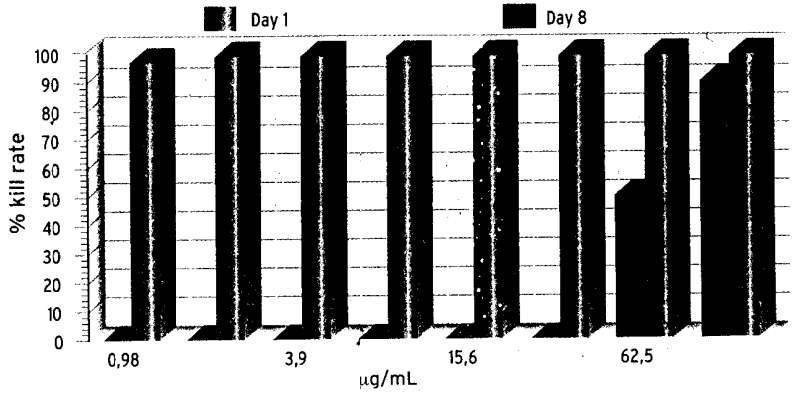



**Table 12**

Fungicidal activity of ciclopirox (non-proliferating conditions)

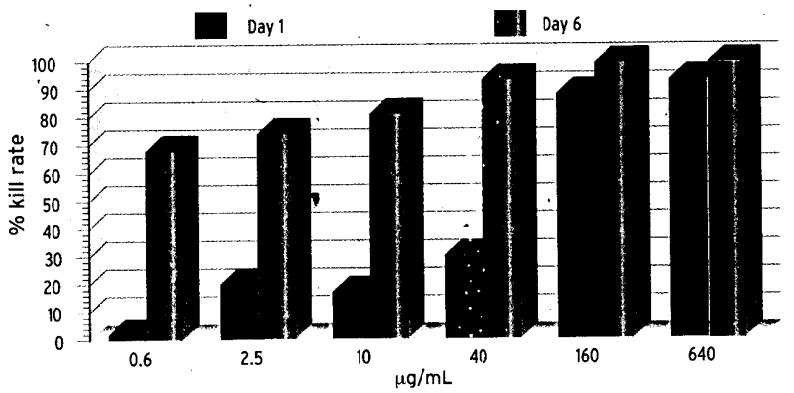


**Table 13**

Topical anti-inflammatory activity in Arachadonic Acid-induced Ear Edema Assay

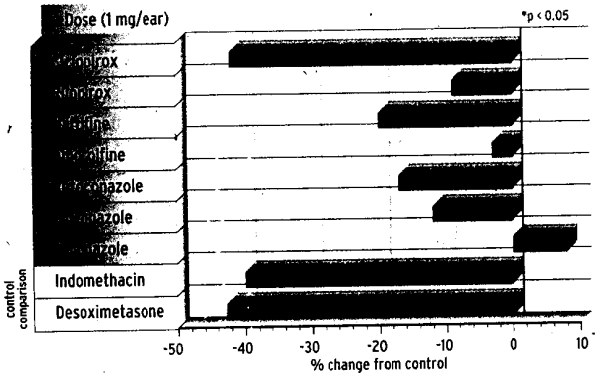
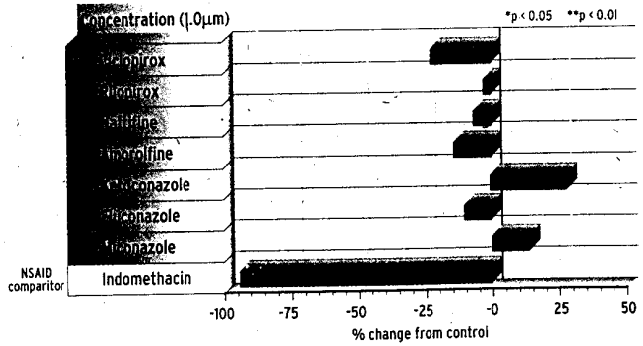





**Table 14**

Modulation of cyclooxygenase metabolite[12] ($PGE_2$) cellular release




## Anti-Inflammatory Effects

Ciclopirox achieves a quick mycological cure while providing rapid symptomatic relief through its anti-inflammatory action. In each of two standard laboratory tests of anti-inflammatory activity, ciclopirox demonstrated greater activity than antifungal comparators. In one study using the Arachadonic Acid-induced Ear Edema Assay, ciclopirox reduced ear edema by over 40% from control. This was a rate more than double that seen with naftifine, ketoconazole, fluconazole or miconazole but similar to the positive controls indomethacin (a non-steroidal, anti-inflammatory compound) and desoximetasone (a steroid).[12] (Table 13)

A second laboratory study, the Modulation of $PGE_2$ (cyclooxygenase metabolite) Release, supports the inherent anti-inflammatory properties of ciclopirox. In this study, ciclopirox caused a significant reduction (25%) in $PGE_2$ release. Comparatively, naftifine and fluconazole caused minimal reduction in $PGE_2$ release, while ketoconazole and miconazole demonstrated no anti-inflammatory activity in this test.[12] (Table 14)

In an *in vivo* human study of exposure to ultraviolet B (UVB), ciclopirox was associated with a higher rate of anti-inflammatory activity than any of the other antifungal preparations tested: naftifine, terbinafine, ketoconazole, oxiconazole, econazole or 2.5% hydrocortisone, a known anti-inflammatory preparation. The differences between ciclopirox and the azole compounds tested were statistically significant.[13] (Table 15)

In another clinical study (n=138), 21 days of b.i.d., ciclopirox mono-therapy demonstrated efficacy in inflamed mycoses equivalent to the combination of ciclopirox plus a 1% hydrocortisone. Ciclopirox was found to inhibit cyclooxygenase and 5-lipoxygenase enzymes that are critical to the inflammatory process. This finding is of clinical importance, since it means that ciclopirox affords patients an antifungal treatment alternative with inherent anti-inflammatory effects that is safer than corticosteroid therapy.[14] (Table 16)

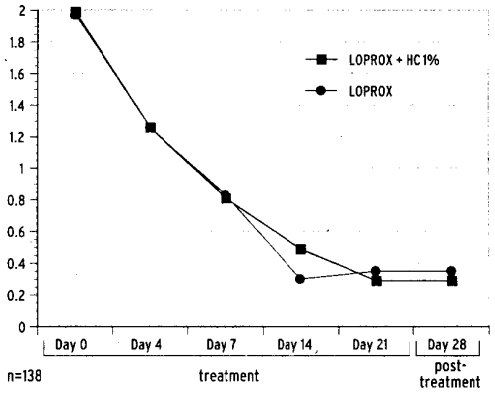
**Table 15**

Anti-inflammatory activity of antifungal cream formulations[13]

| Erythema scores following 2 MED UVB Exposure (0= no erythema to 5= severe erythema) | |
|---|---|
| **Variable** | **Mean** |
| Ciclopirox | 2.15 |
| Naftifine | 2.40 |
| Terbinafine | 2.50 |
| Ketoconazole | 2.95 |
| Oxiconazole | 3.45 |
| Econazole | 3.60 |
| Hydrocortisone | 3.85 |
| Control | 4.30 |

**Table 16**

Mean scores for major signs/symptoms of inflammation[11]
(0= none; 1= mild; 2= moderate; 3= severe; 4= very severe)




# Safety and Adverse Events

Ciclopirox provides the patient a broad-range antifungal treatment with a solid safety profile. LOPROX® (ciclopirox) does not contain propylene glycol, a potential irritant.

In all controlled clinical studies, patients using ciclopirox cream (total n=514), and in 296 patients using the vehicle cream, the incidence of adverse reactions was low. Adverse reactions included pruritus at the application site in one patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in one patient and worsening of the clinical signs and symptoms in another patient using the vehicle cream.[2]

## Contraindications

LOPROX® (ciclopirox) is contraindicated in individuals who have shown hypersensitivity to any of its components.[2]

## Dosage & Administration

Gently massage LOPROX Cream or Lotion into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with the relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of ciclopirox treatment, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment. [2]



## How Supplied

LOPROX Cream is supplied in 15 gram (NDC 99207-009-15 formerly NDC 0039-0009-15), 30 gram (NDC 99207-009-30 formerly NDC 0039-0009-30), and 90 gram (NDC 99207-009-90 formerly NDC 0039-0009-90) tubes. LOPROX Cream should be stored between 59° and 86° F (15° and 30°C).[2]

LOPROX Lotion is supplied in 30 mL (NDC 99207-008-30 formerly NDC 0039-0191-30) and 60 mL (NDC 99207-008-60 formerly NDC (0039-0191-06) bottles. Bottle space provided to allow for vigorous shaking before each use. LOPROX Lotion should be stored between 41° and 77°F (5° and 25°C).[2]

*For additional information regarding LOPROX® (ciclopirox) Cream or Lotion, please write or call:*

MEDICIS, The Dermatology Company®
4343 East Camelback Rd.
Phoenix, AZ 85018
phone: (800) 550-5115
email: marketing@medicis.com
website: www.info@medicis.com

# References


1. Market Measures Inc., Livingston, NJ. Antifungal Drug Study XII. August 1997.
2. LOPROX® (ciclopirox) 0.77% package insert.
3. Abrams BB, Hänel H, Hoehler T. Ciclopirox olamine: a hydroxypyridone antifungal agent. *Clin Dermatol* 1992; 9:471-477.
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5. Hänel H, Raether W, Dittmar W. Evaluation of fungicidal action *in vitro* and in a skin model considering the influence of penetration kinetics of various standard antimycotics. *Ann NY Acad Sci* 1998; 544:329-337.
6. Dittmar W, et al. Microbiological laboratory studies with ciclopirox olamine. *Arzneimittel-Forschung* 1981; 31:1317-1322.
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14. Lassus A, Nolting KS, Savopoulos C. Comparison of ciclopirox olamine 1% cream with ciclopirox 1%-hydrocortisone acetate 1% cream in the treatment of inflamed superficial mycoses. *Clin Ther* 1988; 10(5):594-599.

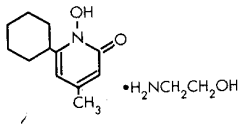

## Additional Sources


Przekop PA, et al. Ciclopirox olamine, an antifungal modulator of neutrophil function and infiltrate in cutaneous inflammation. *J Invest Dermatol* 1994; 102(4):593-599, abs 420.

# Prescribing Information

LOPROX®
(ciclopirox olamine)
Cream .77%
Lotion .77%
**FULL PRESCRIBING INFORMATION**
**FOR DERMATOLOGIC USE ONLY.**
**NOT FOR USE IN EYES.**

**DESCRIPTION**
LOPROX (ciclopirox olamine) Cream .77% and Lotion .77% are for topical use.
Each gram of LOPROX Cream contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of purified water USP, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative.
Each gram of LOPROX Lotion contains 7.70 mg ciclopirox ( as ciclopirox olamine) in a water miscible lotion base consisting of purified water USP, cocamide DEA, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative.
LOPROX Cream and Lotion contain a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt.
The CAS Registry Number is 41621-49-2.
The chemical structure is:




LOPROX Cream 1% and Lotion 1% have a pH of 7.

**CLINICAL PHARMACOLOGY**
Ciclopirox olamine is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur.* Ciclopirox exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida albicans.*

Pharmacokinetic studies in men with tagged ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm2 on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.
Penetration studies in human cadaverous skin from the back, with LOPROX (ciclopirox olamine) Cream with tagged ciclopirox showed the presence of 0.8 to 1.6% of the dose in the stratum corneum 1.5 to 6 hours after application. The levels in the dermis were still 10 to 15 times above the minimum inhibitory concentrations.
Autoradiographic studies with human cadaverous skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.
Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and Photo-Draize study conducted in total of 142 healthy male subjects showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photo-contact sensitization due to LOPROX Cream.
*In vitro* penetration studies in frozen or fresh excised human cadaver and pig skin indicated that the penetration of LOPROX (ciclopirox) Lotion is equivalent to that of LOPROX Cream.
Therapeutic equivalence of cream and lotion formulations also was indicated by studies of experimentally induced guinea pig and human trichophytosis.

**INDICATIONS AND USAGE**
LOPROX Cream and Lotion are indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis;* candidiasis (moniliasis) due to *Candida albicans;* and tinea (pityriasis) versicolor due to *Malassezia furfur.*

**CONTRAINDICATIONS**
LOPROX Cream and Lotion is contraindicated in individuals who have shown hypersensitivity to any of its components.

**WARNINGS**
General: LOPROX (ciclopirox) Cream and Lotion are not for ophthalmic use.

**PRECAUTIONS**
If a reaction suggesting sensitivity or chemical irritation should occur with the use of LOPROX Cream or Lotion, treatment should be discontinued and appropriate therapy instituted.

**Information for Patients**

The patient should be told to:

1. Use the medication for the full treatment time even though signs/symptoms may have improved and notify the physician if there is no improvement after four weeks.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

A carcinogenicity study in female mice dosed cutaneously twice per week for 50 weeks followed by a 6-month drug-free observation period prior to necropsy revealed no evidence of tumors at the application site.

The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olamine: studies to evaluate gene mutation in the Ames *Salmonella*/Mammalian Microsome Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Lethal Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative).

The following battery of *in vitro* genotoxicity tests were conducted with *ciclopirox*: a chromosome aberration assay in V79 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assay in the HGPRT - test with V79 Chinese Hamster Cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA Synthesis Assay in A549 Human Cells (negative)). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cytogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

**Pregnancy Category B**

Reproduction studies have been performed in the mouse, rat, rabbit, and monkey, (via various routes of administration) at doses 10 times or more the topical human dose and have revealed no significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOPROX (ciclopirox) Cream or Lotion is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

**ADVERSE REACTIONS**

In all controlled clinical studies with 514 patients using LOPROX Cream and in 296 patients using the vehicle cream, the incidence of adverse reactions was low. This included pruritus at the site of application in one patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in one patient and worsening of the clinical signs and symptoms in another patient using the vehicle cream.

In the controlled clinical trial with 89 patients using LOPROX Lotion and 89 patients using the vehicle, the incidence of adverse reactions was low. Those considered possibly related to treatment or occurring in more than one patient were pruritus, which occurred in two patients using ciclopirox lotion and one patient using the lotion vehicle, and burning, which occurred in one patient using ciclopirox lotion.

**DOSAGE AND ADMINISTRATION**

Gently massage LOPROX Cream or Lotion into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of treatment with LOPROX Cream or Lotion, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

**HOW SUPPLIED**

LOPROX Cream is supplied in 15 gram (NDC 99207-009-15), 30 gram (NDC 99207-009-30), and 90 gram (NDC 99207-009-90) tubes. Store between 59°and 86°F (15° and 30°C).

LOPROX Lotion is supplied in 30 mL bottles (NDC 99207-008-30) and 60 mL bottles (NDC 99207-008-60).

Bottle space provided to allow for vigorous shaking before each use. Store between 41° and 77°F (5°and 25° C).

Caution: Federal law prohibits dispensing without prescription.

MANUFACTURED SPECIALLY FOR:
MEDICIS, The Dermatology Company®
By: Hoechst Marion Roussell, Inc.

## Concomitant Therapy

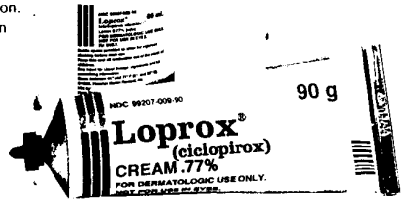
The unique mode of action of LOPROX offers the ability to attack fungal infections from more than one path when concomitant oral and topical therapy is warranted.

## Proven Safety Profile

Clinical studies show a low incidence (0.5%) of adverse reactions to LOPROX. The most common adverse reactions that have been reported are pruritus and burning at the site of application. Contains no propylene glycol. See full prescribing information for further details.

# LOPROX®
## (ciclopirox)

Cream .77% or Lotion .77%




LOPROX cream is available in 15, 30 and 90g tubes. LOPROX lotion is available in 30 and 60mL squeeze bottles.

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Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

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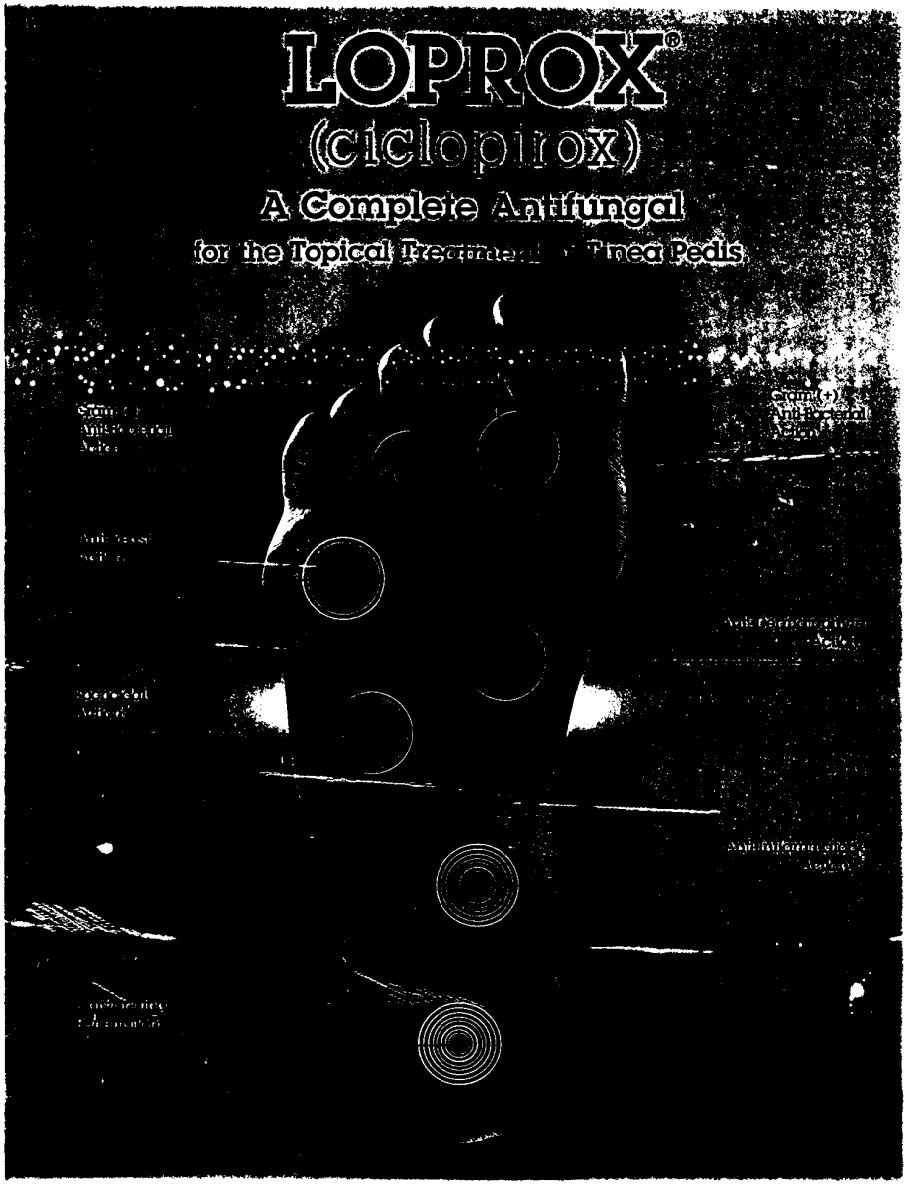
**Caution:** Federal law prohibits dispensing without prescription.

Manufactured specially for: MEDICIS, The Dermatology Company®
BY: HOECHST MARION ROUSSEL INC.

MEDICIS
The Dermatology Company®
800-550-5115



TPY17B00



# LOPROX®
# (ciclopirox)
## A Complete Antifungal
### for the Topical Treatment of Tinea Pedis.

## Redefining Broad-Spectrum

- FUNGISTATIC and FUNGICIDAL against dermatophytes and yeasts[1]
- ANTIBACTERIAL against a host of gram (+) and gram (–) organisms at low MICs[1,2]
- SPORICIDAL, demonstrated activity against non-proliferative phases[2]
- ANTI-INFLAMMATORY effect demonstrated in clinical trials[1,3]

## Clinical Improvement After 1 Week of LOPROX Treatment[4]


## Unique Mode of Action

LOPROX — the only hydroxypyridone antifungal — provides a unique mode of action[1] that:

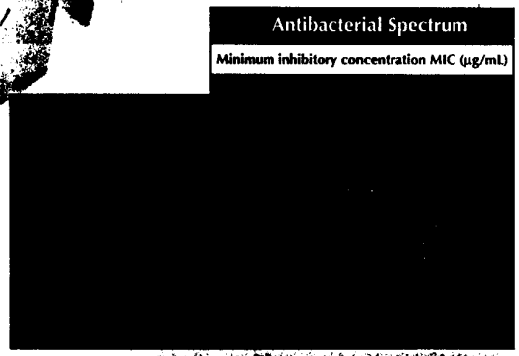
- kills the cell through effect on iron dependent enzyme systems (cytochromes, catalase, peroxidase)
- impairs metabolic activities, transport mechanisms and cell respiratory processes

## Antibacterial

Active against gram (+) and gram (–) bacteria at low MICs when treating mixed infections common in interdigital tinea pedis.[1,2]

Correlation between *in vivo* antimicrobial effect and clinical outcome has not been established. Microbial data establish microbial effect only.

The most common adverse reactions that have been reported are pruritus and burning at the site of application. See full prescribing information for further details.



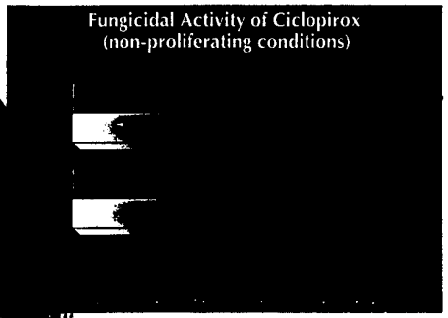

References: 1) Abrams B, et al. Ciclopirox Olamine: A Hydroxypyridone Antifungal Agent. *Clinics in Dermatology* 1992; 9:471-472. 2) Data on file at MEDICIS Pharmaceutical Corp. 3) Lopez A, et al. Comparison of Ciclopirox Olamine 1% Cream with Ciclopirox 1% - Hydrocortisone Acetate 1% Cream in the Treatment of Inflamed Superficial Mycoses. *Clinical Therapeutics* 1988; 10:394-399. 4) Klippert A, Mayser A, et al. Evaluation of Ciclopirox Olamine Cream for the Treatment of Tinea Pedis: Multicenter, Double-Blind Comparative Studies. *Clinical Therapeutics* 1985; 7:409-417. 5) Hänel H, et al. Evaluation of Fungicidal Action in Vitro and in a Skin Model Considering the Influence of Penetration Kinetics of Various Standard Antimycotics. *Annals New York Academy of Sciences* 1990; 544:329-337.

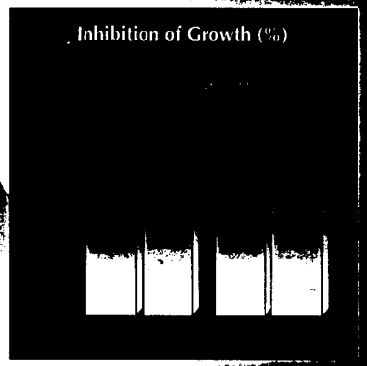
## Sporicidal

Reliable treatment for dormant spores

LOPROX not only treats the growing mycoses, but also is active against non-proliferative phases.

At concentrations as low as 2.5 µg/mL, LOPROX kills >70% of fungal spores by day 6 of treatment with some activity seen within 24 hours. With increasing concentration, the kill rate reaches nearly 100% of non-proliferating fungal phases.




## Superior Penetration Combined with Steep Dose-Response Curve

LOPROX penetrates quickly and deeply to kill pathogenic fungi.

Studies show LOPROX is superior to econazole in inhibitory and fungicidal activity at the level of the stratum corneum (the lowest layer of the stratum corneum nearest the living epidermis).[5]

LOPROX has a very steep dose-response curve. At low concentrations — 3.9 µg/mL to 15.6 µg/mL — LOPROX shows full growth inhibiting capacity.[2]

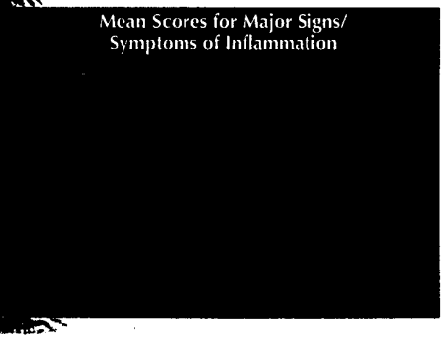
Correlation between *in vivo* antimicrobial effect and clinical outcome has not been established. Microbial data establish microbial effect only.

## Anti-Inflammatory Effect Equivalent to Mild Corticosteroid

Study shows that the addition of [illegible] increase the anti-inflammatory effect compared to LOPROX alone when treating inflammatory fungal infections.

LOPROX is a reliable treatment for inflammatory mycoses without the additional risks of corticosteroid side effects.

Not for ophthalmic use.




**LOPROX (CICLOPIROX) REDEFINES THE SCOPE OF BROAD-SPECTRUM TOPICAL ANTI-FUNGAL TREATMENT.**

Its unique mode of action makes LOPROX effective against a wide range of cutaneous mycoses[1]. LOPROX has demonstrated activity against both dermatophytes and yeasts[1] as well as the proliferative and nonproliferative phases of fungal organisms[2]. This sporicidal activity may reduce the possibility of recurrent infection.[3–6] LOPROX is active against both gram-positive and gram-negative bacteria, making it ideally suited for mixed infections. In addition, LOPROX has anti-inflammatory activity equivalent to a mild steroid[7].

So, you have a choice. You can either let cutaneous mycoses off lightly. Or, you can prescribe LOPROX and send them to their death.

**LOPROX®**
(ciclopirox) Cream or Lotion

MEDICIS
The Dermatology Company®

**References: 1)** Abrams B., et al. Ciclopirox Olamine: A Hydroxypyridone Antifungal Agent. *Clinics in Dermatology* 1992; 9:471-477. **2)** Data in File. **3)** Kligman A.M., et al. Evaluation of Ciclopirox Olamine Cream for the Treatment of Tinea Pedis: Multicenter, Double-Blind Comparative Studies. *Clinical Therapeutics* 1985; 7:409-417. **4)** Cullen S.I., et al. Treatment of Tinea Versicolor with a New Antifungal Agent, Ciclopirox Olamine Cream 1%. *Clinical Therapeutics* 1985; 7:574-583. **5)** Bogaert H., et al. Multicentre Double-Blind Clinical Trials of Ciclopirox Olamine Cream 1% in the Treatment of Tinea Corporis and Tinea Cruris. *J Int Med Res* 1986; 14:210-216. **6)** Bogatell F.K., et al. Evaluation of a New Antifungal Cream, Ciclopirox Olamine 1% in the Treatment of Cutaneous Candidiosis. *Clinical Therapeutics* 1985; 8:41-48. **7)** Lassus A., et al. Comparison of Ciclopirox Olamine 1% Cream with Ciclopirox 1% - Hydrocortisone Acetate 1% Cream in the Treatment of Inflamed Superficial Mycoses. *Clinical Therapeutics* 1988; 10:594-599.

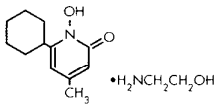
# LOPROX®
(ciclopirox) Cream or Lotion

## FULL PRESCRIBING INFORMATION

**FOR DERMATOLOGIC USE ONLY.**
**NOT FOR USE IN EYES.**

### DESCRIPTION

LOPROX (ciclopirox) Cream 0.77% and Lotion 0.77% are for topical use.
Each gram of LOPROX Cream contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of purified water USP, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative.
Each gram of LOPROX Lotion contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water miscible lotion base consisting of purified water USP, cocamide DEA, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative.
LOPROX Cream and Lotion contain a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(*1H*)-pyridone, 2-aminoethanol salt.
The CAS Registry Number is 41621-49-2.
The chemical structure is:




LOPROX Cream 1% and Lotion 1% have a pH of 7.

### CLINICAL PHARMACOLOGY

Ciclopirox is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur*. Ciclopirox exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida albicans.*
Pharmacokinetic studies in men with tagged ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 $cm^2$ on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application, only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.
Penetration studies in human cadaverous skin from the back, with LOPROX (ciclopirox) Cream with tagged ciclopirox showed the presence of 0.8 to 1.6% of the dose in the stratum corneum 1.5 to 6 hours after application. The levels in the dermis were still 10 to 15 times above the minimum inhibitory concentrations.
Autoradiographic studies with human cadaverous skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.
Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and Photo-Draize study conducted in the total of 142 healthy male subjects showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photo-contact sensitization due to LOPROX Cream.
*In vitro* penetration studies in frozen or fresh excised human cadaver and pig skin indicated that the penetration of LOPROX (ciclopirox) Lotion is equivalent to that of LOPROX Cream. Therapeutic equivalence of cream and lotion formulations also was indicated by studies of experimentally induced guinea pig and human trichophytosis.

### INDICATIONS AND USAGE

LOPROX Cream and Lotion are indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis; candidiasis* (moniliasis) due to *Candida albicans;* and tinea (pityriasis) versicolor due to *Malassezia furfur.*

### CONTRAINDICATIONS

LOPROX Cream and Lotion are contraindicated in individuals who have shown hypersensitivity to any of their components.

### WARNINGS

General:
LOPROX (ciclopirox) Cream and Lotion are not for ophthalmic use.

### PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of LOPROX Cream or Lotion, treatment should be discontinued and appropriate therapy instituted.

**Information for Patients**
The patient should be told to:
1. Use the medication for the full treatment time even though signs/symptoms may have impro and notify the physician if there is no improvement after four weeks.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
A carcinogenicity study in female mice dosed cutaneously twice per week for 50 weeks follow by a 6-month drug-free observation period prior to necropsy revealed no evidence of tumors a application site.
The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olami studies to evaluate gene mutation in the Ames *Salmonella*/Mammalian Microsome Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Leth Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative). The following battery *vitro* genotoxicity tests were conducted with *ciclopirox*: a chromosome aberration assay in V7 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assa the HGPRT - test with V79 Chinese Hamster Cells (negative); and a primary DNA damage ass (i.e., unscheduled DNA Synthesis Assay in A549 Human Cells (negative)). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cytogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

**Pregnancy Category B**
Reproduction studies have been performed in the mouse, rat, rabbit, and monkey, (via various routes of administration) at doses 10 times or more the topical human dose and have revealed significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, how no adequate or well-controlled studies in pregnant women. Because animal reproduction studi are not always predictive of human response, this drug should be used during pregnancy only clearly needed.

**Nursing Mothers**
It is not known whether this drug is excreted in human milk. Because many drugs are excretec in human milk, caution should be exercised when LOPROX (ciclopirox) Cream or Lotion is administered to a nursing woman.

**Pediatric Use**
Safety and effectiveness in pediatric patients below the age of 10 years have not been establis

### ADVERSE REACTIONS

In all controlled clinical studies with 514 patients using LOPROX Cream and in 296 patients u the vehicle cream, the incidence of adverse reactions was low. This included pruritus at the sit application in one patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in one patient and worsening of the clinical signs and symp in another patient using the vehicle cream.
In the controlled clinical trial with 89 patients using LOPROX Lotion and 89 patients using the veh the incidence of adverse reactions was low. Those considered possibly related to treatment or occurring in more than one patient were pruritus, which occurred in two patients using ciclopir lotion and one patient using the lotion vehicle, and burning, which occurred in one patient usi ciclopirox lotion.

### DOSAGE AND ADMINISTRATION

Gently massage LOPROX Cream or Lotion into the affected and surrounding skin areas twice in the morning and evening. Clinical improvement with relief of pruritus and other symptoms us occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of treatment with LOPROX Cream or Lotion, the diagnosis should be redetermined. Pati with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatm

### HOW SUPPLIED

LOPROX Cream is supplied in 15 gram (NDC 99207-009-15), 30 gram (NDC 99207-009-3( and 90 gram (NDC 99207-009-90) tubes.
Store between 59° and 86° F (15° and 30° C).
LOPROX Lotion is supplied in 30 mL bottles (NDC 99207-008-30) and 60 mL bottles (NDC 99207-008-60).
**Bottle space provided to allow for vigorous shaking before each use.**
Store between 41° and 77° F (5° and 25° C).
**Caution:** Federal law prohibits dispensing without prescription.

Manufactured specially for:
MEDICIS, The Dermatology Company®
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