PRODUCT MONOGRAPH

LOPROX® CREAM
(Ciclopirox olamine Cream, USP, 1%)

LOPROX® LOTION
(Ciclopirox olamine Lotion, 1%)

Topical Antifungal Agent

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PHARMACOLOGIC CLASSIFICATION

Topical Antifungal Agent

ACTIONS AND CLINICAL PHARMACOLOGY

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

The mode of action of ciclopirox olamine was studied mainly in *Candida albicans*. It is presumed that ciclopirox olamine mediated growth inhibition or death of fungal cells is primarily caused by *in-vitro* cellular depletion of some essential substrates and/or ions and that such effects are brought about through blockage of their uptake from the medium.

No data on mechanism of action are available for dermatophytes.

INDICATIONS AND CLINICAL USE

LOPROX® (ciclopirox olamine) Cream or Lotion is 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, Microsporum canis; cutaneous candidiasis (moniliasis) due to *Candida albicans*; and tinea (pityriasis) versicolor due to Malassezia furfur.

LOPROX® (ciclopirox olamine) Cream or Lotion is not proposed for vaginal application.

CONTRAINDICATIONS

LOPROX® (ciclopirox olamine) Cream or Lotion is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

LOPROX® (ciclopirox olamine) Cream or Lotion is not for ophthalmic use.

PRECAUTIONS

General

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

Use in Pregnancy

Reproduction studies have been performed in the mouse, rat, rabbit and monkey (via various routes of administration) at doses 10 times or greater than the topical human dose. No significant evidence of impaired fertility or harm to the fetus due to the use of ciclopirox olamine has been revealed. However, a higher incidence of systemic absorption of ciclopirox olamine in the rat was noted in the group given 30 mg/kg orally as compared to controls. 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.

Use in 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 olamine) Cream or Lotion is administered to nursing women.

Use in Children

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

ADVERSE REACTIONS

LOPROX® (ciclopirox olamine) Cream and Lotion are well tolerated with a low incidence of adverse reactions reported in clinical trials. LOPROX® Cream had a 0.4% incidence of adverse reactions in controlled clinical trials. These included pruritus at the site of application, worsening of clinical signs and symptoms and mild to severe burning reported in a few cases.

In a controlled clinical trial with 89 patients using LOPROX® Lotion and 89 patients using the vehicle, the incidence of adverse reactions was low. The side effects included pruritus occurring in three patients and burning, which occurred in one patient.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no clinical reports of acute overdosage with LOPROX® (ciclopirox olamine) Cream or Lotion by any route of administration.

From acute toxicity studies of ciclopirox olamine cream 1% in adult rats, oral doses of 36 g/kg produced no evidence of toxic signs. (For further information please refer to Toxicology).

DOSAGE AND ADMINISTRATION

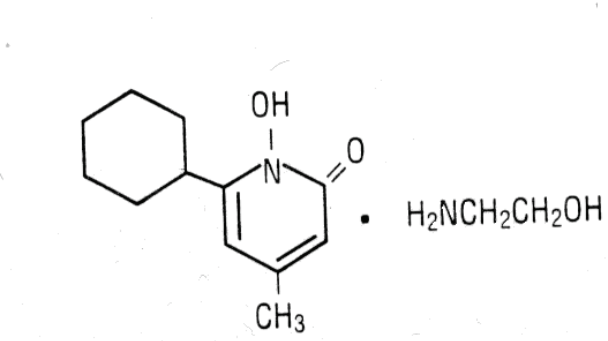
Gently massage LOPROX® (ciclopirox olamine) Cream or Lotion into the affected and surrounding skin areas twice daily, in the morning and evening for a minimum of 4 weeks. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after two weeks of treatment with LOPROX® the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Ciclopirox olamine

Structural Formula:



Molecular Formula: $C_{12}H_{17}NO_2.C_2H_7NO$

Molecular Weight: 268.36

Chemical Name: 6-cyclohexyl-1-hydroxy-4-methyl-2-(1H)-pyridone compound with 2-aminoethanol (1:1)

Description: Ciclopirox olamine is a crystalline powder, white to pale yellow in color. It is soluble in methanol.

Dosage Forms

Composition: LOPROX® Cream is supplied as a formulation containing ciclopirox olamine USP, 1%. Non-medicinal ingredients are: benzyl alcohol NF, cetyl alcohol NF, cocoamide DEA, lactic acid USP, mineral oil USP, myristyl alcohol NF, octyldodecanol NF, polysorbate 60 NF, purified water USP, sorbitan monostearate NF and stearyl alcohol NF.

LOPROX® Lotion is supplied as a formulation containing ciclopirox olamine USP, 1%. Non-medicinal ingredients are: benzyl alcohol NF, cetyl alcohol NF, cocoamide DEA, lactic acid USP, mineral oil USP, myristyl alcohol NF, octyldodecanol NF, polysorbate 60 NF, purified water USP, sorbitan monostearate NF and stearyl alcohol NF.

Ciclopirox olamine is a Schedule F prescription drug.

Availability: LOPROX® Cream is available in tubes of 45 g.
LOPROX® Lotion is available in a 60 mL bottle.

Storage: Store at room temperature, i.e. 15-30°C.

MICROBIOLOGY

Ciclopirox olamine can best be described as a broad spectrum antimycotic agent with significant antibacterial activity. It is also effective against several protozoa.

In-vitro studies were done with the yeast *Candida albicans*. The specific parameters examined included possible effects on (i) osmotic fragility, (ii) respiration, (iii) uptake and incorporation of radioactive leucine and adenine, and (iv) leakage or efflux of intracellular K+ and other materials. These studies show that fungitoxic activity of ciclopirox olamine appears to be attributed to the inhibition of uptake of precursors of macromolecular syntheses from the medium. The drug had a greater inhibitory effect on the uptake and accumulation of leucine in the internal pool of starved cells than it had on subsequent protein synthesis. Ciclopirox olamine was also effective in altering the cell permeability, but greater drug concentrations were required to induce appreciable leakage of cellular constituents, such as 260 nm-absorbing materials, folin-positive substances and potassium ions, from the cells. Osmotic fragility and endogenous respiration were virtually unaffected by the drug. Partial inhibition of the respiratory activity of yeast cells or mitochondria by relatively high concentrations of ciclopirox can therefore be explained by a decreased uptake of exogenous substrates from the medium.

Further studies on the mechanism of the anti-fungal activity of ciclopirox olamine against *Candida albicans* showed that ciclopirox olamine was fungicidal to growing cultures of *Candida albicans*. This effect was apparent only after a certain period of cell proliferation, depending upon the drug concentration. Glucose-dependent uptake of amino acids, K+ and phosphate in starved *Candida albicans* cells was significantly but variably inhibited by the drug at levels around MIC. It is presumed from these results that ciclopirox olamine mediated growth inhibition or death of fungal cells is primarily caused by intracellular depletion of some essential substrates and/or ions and that such effects are brought about through blockage of their uptake from the medium.

The spectrum of ciclopirox olamine activity *in vitro* is given below:

Organism	Minimum Inhibitory Concentration - MIC µg/mL
Fungi:	
Dermatophytes	0.98 - 3.9
Yeast-like fungi	0.98 3.9
Molds	0.49 - 15.6
Actinomycetales	3.9 - 7.8
Bacteria:	
Staphylococcus aureus	12.5 - 15.6
Streptococcus	10.0 - 20.8
Salmonella	15.6 - 41.7
Shigella	10.4 - 20.8
Aerobacter	25.0 - 333.0
Klebsiella pneumonia FHB-50	25.0
Proteus	20.8 - 31.5
Pasteurella	7.8 - 12.5
Corynebacterium	20.8 - 25.0
Listeria monocytogenes FHB-90	15.6
Erysipelothrix-rheusiopathiae FHB-95	15.6
Bacillus	10.4 - 15.6
Pseudomonas	62.5 - 125.0
Protozoa:	
Entamoeba histolytica (1 Strain)	100
Trichomonas vaginalis (6 Strains)	50

The addition of protein to the media had little effect on the MIC of ciclopirox olamine against the most relevant pathogens. Further, pH and the quantity of organism inoculated did not alter the inhibitory action of ciclopirox olamine.

In Vivo

Ciclopirox olamine solution 1% was evaluated in guinea pigs using four pathogens: Trichophyton mentagrophytes (HPV), Trichophyton quincheanum (Zch), Trichophyton verrucosum (Bay), Microsporum canis (559). Significant inhibition of infection was seen. Against Trichophyton mentagrophytes significant inhibitions were observed at concentrations of ciclopirox olamine as low as 0.04%.

No systemic activity of ciclopirox olamine was observed in rodents and dogs against a variety of pathogens.

PHARMACOLOGY

In Vitro

In vitro studies using frozen or fresh excised human cadaver and pig skin indicated that the penetration of ciclopirox olamine lotion 1% is equivalent to that of ciclopirox olamine cream 1%. Therapeutic equivalence of cream and lotion formulations was also indicated by studies of experimentally induced guinea pig and human trichophytosis.
Animal

Animal

General pharmacology studies did not show central nervous system effects of ciclopirox olamine at 80 mg/kg. Further, the compound was not effective in analgesic or anti-inflammatory screen tests in rodents and failed to alter body temperature in rabbits. The lack of pertinent pharmacologic activity was also shown in ciclopirox olamine as a diuretic and *in vitro* using the guinea pig ileum. Changes in blood pressure and heart rate were transient after a dose of 10 mg/kg i.v. to anesthetized dogs and there were no consistent alterations in blood coagulation.

It would appear from the studies listed above, that ciclopirox olamine has little, if any, classical pharmacological effect and that its main action is restricted to antimycotic and antibacterial activity.

Pharmacokinetic studies on the absorption, tissue distribution, detoxification and excretion were carried out in dogs, rabbits and humans.

The oral administration of ciclopirox olamine ^{14}C to dogs (15 mg/kg) resulted in a rapid absorption with maximal blood levels of 2-7.5 µg/mL in 1.5- 2 hours. The drug was distributed mainly to the organs of excretion. Following intravenous administration, excretion followed several phases with half-lives of 1.5 minutes, 1-2 hours and 8-13 hours.

Urinary and fecal excretion accounted for 95-97% of administered drug. Urinary excretion accounted for 35-44% of dose after oral administration and 48-57% of dose after intravenous administration.

After dorsal application, ciclopirox olamine ^{14}C penetrated rabbit skin transepidermally as well as transfollicularly. The stratum corneum appears to be a depot from which small quantities of drug penetrate continually into deeper layers of the skin.

Human

Cadaver

Penetration studies in human cadaverous skin with tagged ciclopirox olamine cream 1% showed the presence of 0.8 and 1.6% of the dose in 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 olamine penetrates through the epidermis, hair follicles, into the dermis, hair, and the sebaceous gland with a "depot" or reservoir in the stratum corneum.

Clinical Pharmacology

Pharmacokinetic studies[1] in males with tagged ciclopirox olamine cream 1% showed an average of 1.3% absorption of the dose. The cream was applied topically under occlusion to the back, with a total penetration time of 6 hours. Excretion occurred via the kidney, with biological half-life of 1.7 hours. Two days after application only 0.01% of the dose applied could be found in the urine.

Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and Photo-Draize study conducted in a 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 ciclopirox olamine cream 1%. The ingredients of ciclopirox olamine lotion 1% are qualitatively the same as those of ciclopirox olamine cream 1%.

TOXICOLOGY

Acute Toxicity

The acute toxicity of ciclopirox olamine was determined orally in mice, rats (adult and neonate) and rabbits and parenterally (subcutaneous, intravenous and intraperitoneal) in mice and rats. The oral and subcutaneous LD_{50}'s ranged from 1 700 to > 2 500 mg/kg in adult mice and rats. The intravenous LD_{50}'s ranged from 71 to 79 mg/kg and the intraperitoneal LD_{50}'s ranged from 83 to 172 mg/kg in adult mice and rats. Principal signs of systemic toxicity included irregular respiration and clonic convulsions. After subcutaneous injection, necrosis was seen at the injection site. In the neonatal rat, the intragastric LD_{50} was 445 mg/kg. Intraperitoneally, neonatal rats tolerated a dose of 20 mg/kg without signs of toxicity. A single topical 24 hour application of 5 mL of a 1% solution of ciclopirox olamine was tolerated by rabbits without effects.

Chronic Toxicity

The subacute and chronic toxicity of ciclopirox olamine was studied in mice, rats, guinea pigs, rabbits, and dogs for various periods of time and by various routes of administration. Oral administration of 10 mg/kg of ciclopirox olamine was tolerated without effects in both rats and dogs for three months. Oral doses of 30 mg/kg and higher in dogs caused mortality and degenerative changes particularly in the heart (necrosis of myocardial fibres) and the liver (toxic yellow atrophy).

Daily dermal application of ciclopirox olamine in concentrations of 1, 3 or 10% in polyethylene glycol 400 to the intact and abraded skin of rabbits for three months and to dogs for six months produced no systemic toxic effects. However, the topical applications caused dose-dependent and time-dependent changes in the skin, including a moderate to pronounced thickening of the stratum germinativum of the epidermis, with hyperkeratosis in the rabbit and parakeratosis in the dog, and a chronic inflammatory reaction in the subepidermal corium. The changes in the skin receded to normal after four to six weeks.

In a 30-day dermal tolerance study on intact and abraded skin of guinea pigs and rabbits, ciclopirox olamine 1% formulation and the aqueous cream base caused some thickening of the epidermis with hyperkeratosis. The reaction was reversible within four weeks.

Carcinogenicity

A carcinogenic study was carried out in mice with concentrations of 1 and 5% compound in polyethylene glycol 400 applied to the intact skin, twice a week, for one year, followed by a six-month period of observation. No tumours were observed in any of the mice at the site of application on the skin. The incidence of neoplasms was similar among control groups.

Mutagenicity

Ciclopirox olamine was devoid of mutagenic activity as demonstrated by several microbial tests, the micronucleus test and the dominant lethal test in mice. In a battery of *in vitro* genotoxicity tests with ciclopirox free acid, one assay was positive; however, the positive findings were not substantiated by *in vivo* testing.

Reproduction and Teratology

Reproduction-teratology studies were performed as follows: fertility and reproduction (Segment I) in the rat; teratology (Segment II) in the mouse, rat, rabbit, and monkey; and perinatal/postnatal (Segment III) in the rat. The routes of administration used were oral, subcutaneous or dermal. Segment I and III studies in rats receiving oral doses of up to 5 mg/kg showed no effects on the various maternal or fetal parameters. Teratological studies in mice, rats, rabbits, and monkeys receiving oral doses of up to 100, 30, 30, or 50 mg/kg, respectively, or in mice and rats receiving subcutaneous doses of up to 10 mg/kg produced no significant fetal malformations. However, some skeletal variations were seen at the higher doses in the oral-rat and the subcutaneous mouse studies. Dermal teratological studies in rats and rabbits receiving topical applications of up to 10% concentrations produced no significant fetal malformations. However, some maternal and fetal toxicity was seen at the highest dose in rats (higher incidence of resorptions in the group given 30 mg/kg as compared to controls).

Other Studies

A phototoxic test carried out in hairless mice demonstrated no evidence of phototoxic properties for the compound.

An eye irritancy test with ciclopirox olamine 1% cream formulation was devoid of irritation in rabbits. In similar tests, the pure compound applied as a dry powder was a severe irritant to the eye. When the compound was applied as a solution in water only minimal irritation was observed.

Tolerance studies of ciclopirox olamine administered intravaginally to dogs for two weeks as a 2% suppository formulation and for five weeks as a 4 mg tablet formulation showed no local or systemic adverse effects.

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