CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-022

FINAL PRINTED LABELING

PENLAC™ NAIL LACQUER (CICLOPIROX) TOPICAL SOLUTION, 8%

FOR USE ON FINGERNAILS AND TOENAILS AND IMMEDIATELY ADJACENT SKIN ONLY

NOT FOR USE IN EYES

CAUTION
Federal Law Prohibits Dispensing Without Prescription

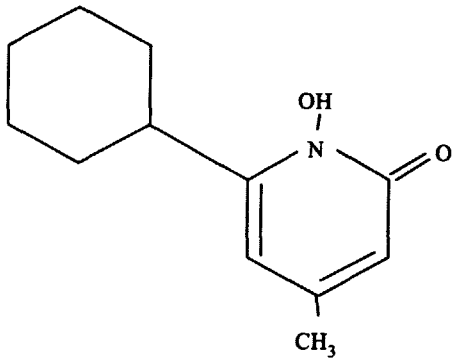
DESCRIPTION

PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, contains a synthetic antifungal agent, ciclopirox. It is intended for topical use on fingernails and toenails and immediately adjacent skin.

Each gram of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, NF; isopropyl alcohol, USP; and butyl monoester of poly[methylvinyl ether/maleic acid] in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application.

PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is a clear, colorless to slightly yellowish solution.

The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27. The CAS Registry Number is [29342-05-0]. The chemical structure is:



CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

The mechanism of action of ciclopirox has been investigated using various *in vitro* and *in vivo* infection models. One *in vitro* study suggested that 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. The clinical significance of this observation is not known.

Activity *in vitro* and *ex vivo*

In vitro methodologies employing various broth or solid media with and without additional nutrients have been utilized to determine ciclopirox minimum inhibitory concentration (MIC) values for the dermatophytic molds [1-2]. As a consequence, a broad range of MIC values, 1-20 ug/mL, were obtained for *Trichophyton rubrum* and *Trichophyton mentagrophytes* species. Correlation between *in vitro* MIC results and clinical outcome has yet to be established for ciclopirox.

One *ex vivo* study was conducted evaluating 8% ciclopirox against new and established *Trichophyton rubrum* and *Trichophyton mentagrophytes* infections in ovine hoof material[3]. After 10 days of treatment the growth of *T. rubrum* and *T. mentagrophytes* in the established infection model was very minimally affected. Elimination of the molds from hoof material was not achieved in either the new or established infection models.

Susceptibility testing for *Trichophyton rubrum* species

In vitro susceptibility testing methods for determining ciclopirox MIC values against the dermatophytic molds, including *Trichophyton rubrum* species, have not been standardized or validated. Ciclopirox MIC values will vary depending on the susceptibility testing method employed, composition and pH of media and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *Trichophyton rubrum* are susceptible or resistant to ciclopirox have not been established.

Resistance

Studies have not been conducted to evaluate drug resistance development in *T. rubrum* species exposed to 8% ciclopirox topical solution. Studies assessing cross-resistance to ciclopirox and other known antifungal agents have not been performed.

Antifungal Drug Interactions

No studies have been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents for onychomycosis.

Therefore, the concomitant use of 8% ciclopirox topical solution and systemic antifungal agents for onychomycosis, is not recommended.

Pharmacokinetics

As demonstrated in pharmacokinetic studies in animals and man, ciclopirox olamine is rapidly absorbed after oral administration and completely eliminated in all species via feces and urine. Most of the compound is excreted either unchanged or as glucuronide. After oral administration of 10 mg of radiolabeled drug (14C-ciclopirox) to healthy volunteers, approximately 96% of the radioactivity was excreted renally within 12 hours of administration. Ninety-four percent of the renally excreted radioactivity was in the form of glucuronides. Thus, glucuronidation is the main metabolic pathway of this compound.

Systemic absorption of ciclopirox was determined in 5 patients with dermatophytic onychomycoses, after application of PENLAC™ NAIL LACQUER Topical Solution, 8%, to all 20 digits and adjacent 5 mm of skin once daily for six months. Random serum concentrations and 24 hour urinary excretion of ciclopirox were determined at two weeks and at 1, 2, 4 and 6 months after initiation of treatment and 4 weeks post-treatment. In this study, ciclopirox serum levels ranged from 12-80 ng/mL. Based on urinary data, mean absorption of ciclopirox from the dosage form was <5% of the applied dose. One month after cessation of treatment, serum and urine levels of ciclopirox were below the limit of detection.

In two vehicle-controlled trials, patients applied PENLAC™ NAIL LACQUER Topical Solution, 8%, to all toenails and affected fingernails. Out of a total of 66 randomly selected patients on active treatment, 24 had detectable serum ciclopirox concentrations at some point during the dosing interval (range 10.0-24.6 ng/mL). It should be noted that eleven of these 24 patients took concomitant medication containing ciclopirox as ciclopirox olamine (Loprox® Cream, 0.77%).

The penetration of the PENLAC™ NAIL LACQUER Topical Solution, 8%, was evaluated in an *in vitro* investigation. Radiolabeled ciclopirox applied once to onychomycotic toenails that were avulsed demonstrated penetration up to a depth of approximately 0.4 mm. As expected, nail plate concentrations decreased as a function of nail depth. The clinical significance of these findings in nail plates is unknown. Nail bed concentrations were not determined.

INDICATIONS AND USAGE

(To understand fully the indication for this product, please read the entire INDICATION AND USAGE section of the labeling.)

PENLAC™ NAIL LACQUER Topical Solution, 8%, as a component of a comprehensive management program, is indicated as topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and

toenails without lunula involvement, due to *Trichophyton rubrum*. The comprehensive management program includes removal of the unattached, infected nails as frequently as monthly, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures.

- No studies have been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents for onychomycosis. Therefore, the concomitant use of 8% ciclopirox topical solution and systemic antifungal agents for onychomycosis, is not recommended.

- PENLAC™ NAIL LACQUER Topical Solution, 8%, should be used only under medical supervision as described above.

- The effectiveness and safety of PENLAC™ NAIL LACQUER Topical Solution, 8%, in the following populations has not been studied. The clinical trials with use of PENLAC™ NAIL LACQUER Topical Solution, 8%, excluded patients who: were pregnant or nursing, planned to become pregnant, had a history of immunosuppression (e.g., extensive, persistent, or unusual distribution of dermatomycoses, extensive seborrheic dermatitis, recent or recurring herpes zoster, or persistent herpes simplex), were HIV seropositive, received organ transplant, required medication to control epilepsy, were insulin dependent diabetics or had diabetic neuropathy. Patients with severe plantar (moccasin) tinea pedis were also excluded.

- The safety and efficacy of using PENLAC™ NAIL LACQUER Topical Solution, 8%, daily for greater than 48 weeks have not been established.

Clinical Trials Data:

The results of use of PENLAC™ NAIL LACQUER Topical Solution, 8%, in treatment of onychomycosis of the toenail without lunula involvement were obtained from two double-blind, placebo-controlled studies conducted in the US. In these studies, patients with onychomycosis of the great toenails without lunula involvement were treated with ciclopirox topical solution, 8%, in conjunction with monthly removal of the unattached, infected toenail by the investigator. PENLAC™ NAIL LACQUER Topical Solution, 8%, was applied for 48 weeks. At baseline, patients had 20–65% involvement of the target great toenail plate. Statistical significance was demonstrated in one of two studies for the endpoint "complete cure" (clear nail and negative mycology), and in two studies for the endpoint "almost clear" (≤10% nail involvement and negative mycology) at the end of study. These results are presented below.

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