PRODUCT MONOGRAPH

PrPENLAC®
Ciclopirox Topical Solution
8% w/w

Nail Lacquer
Topical Antifungal Agent

Bausch Health, Canada Inc.
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Laval, Quebec
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PRODUCT MONOGRAPH

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Ciclopirox Topical Solution
8% w/w

ACTIONS AND CLINICAL PHARMACOLOGY

Ciclopirox free acid is an antimycotic agent that inhibits the growth of a number of fungi *in vitro* including *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, *Epidermophyton floccosum*, *Candida albicans*, *Candida tropicalis* and *Candida pseudotropicalis*.

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.

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 radiolabelled drug (^{14}C-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 (Ciclopirox Topical Solution, 8% w/w) nail lacquer, 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 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).

The penetration of PENLAC 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. 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 CLINICAL USE

Please read this entire section carefully to fully understand the indication for this product.

Topical treatment with PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer is indicated as part of a comprehensive nail management program in immunocompetent patients with mild to moderate onychomycosis (due to *Trichophyton rubrum)* of fingernails and toenails without lunula involvement. The comprehensive management program includes frequent removal of unattached, infected nails (e.g., monthly) by a health care professional with special competence in the diagnosis and treatment of nail disorders, including minor nail procedures. PENLAC should therefore be used only under medical supervision. The safety and efficacy of daily use for longer than 48 weeks have not been established (see PRECAUTIONS.)

Pivotal Clinical Trial Data

PENLAC was used to treat onychomycosis of the great toenail (without lunula involvement) in two double-blind, placebo-controlled pivotal studies. Patients were treated once daily for up to 48 weeks in conjunction with monthly removal of the unattached infected toenail by the investigator. At baseline, patients had 20-65% involvement of the target nail plate.

Endpoint ITT Population

Efficacy Variable	Study 312‡		Study 313‡	
	Ciclopirox	Placebo	Ciclopirox	Placebo
Treatment Success[1]	8/107 (8%)	1/107 (1%)	13/115 (11%)	1/115 (1%)
Treatment Cure[2]	6/110 (6%)†	1/109 (1%)	10/118 (9%)	0/117 (0%)
Mycological Cure[3]	30/105 (29%)	14/105 (13%)	39/113 (35%)	10/114 (9%)

1 Treatment Success: *negative culture, negative KOH, ≤10% involvement target nail*
2 Treatment Cure: *negative culture & KOH, Global Evaluation Score = Cleared*
3 Mycological Cure: *negative culture, negative KOH*
‡ Denominators differ across variables because of missing data
†p = 0.055. All other values statistically significant (CMH≤0.02, stratified by centre)

Post-treatment efficacy assessments were scheduled only for patients who achieved treatment cure. Some data on the post-treatment efficacy of the product are available for 12 patients. Twelve weeks after stopping ciclopirox treatment, 3/6 patients-maintained treatment success, and 6/9 patients maintained negative mycology reports.

CONTRAINDICATIONS

PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer is not for ophthalmic, oral, or intravaginal use. For use on nails and immediately adjacent skin only.

PRECAUTIONS

No studies have been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents for onychomycosis. Therefore, the concomitant use of PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer and systemic antifungal agents for onychomycosis, is not recommended (see INDICATIONS AND CLINICAL USE.)

The effectiveness and safety in the following populations have not been studied, as the clinical trials with PENLAC 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.

So far there is no relevant clinical experience with patients with insulin dependent diabetes or who have diabetic neuropathy. The risk of removal of the unattached, infected nail, by the health care professional and trimming by the patient should be carefully considered before prescribing to patients with a history of insulin dependent diabetes mellitus or diabetic neuropathy.

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

Use in Pregnancy
Teratology studies in mice, rats, rabbits, and monkeys at oral doses of up to 77, 23, 23, or 38.5 mg, respectively, of ciclopirox as ciclopirox olamine/kg/day, or in rats and rabbits receiving topical doses of up to 92.4 and 77 mg/kg/day, respectively, did not indicate any significant fetal malformations.

Teratology studies with ciclopirox free acid were performed in rats with oral doses of 20, 50, or 125 mg/kg/day and in rabbits with oral doses of 12.5, 32, or 80 mg/kg/day; no significant fetal malformations were noted.

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. PENLAC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when PENLAC is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Vehicle-controlled clinical trials of PENLAC conducted in the US did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

Information to Be Provided to Patients

Patients should be provided with instructions regarding the use of PENLAC (see INFORMATION FOR THE PATIENT).

The patient should be told:

1. To avoid contact with the eyes and mucous membranes. Contact with skin other than skin immediately surrounding the treated nail(s) should be avoided. PENLAC is for external use only.

2. To apply PENLAC evenly over the entire nail plate and 5 mm of surrounding skin. If possible, PENLAC should be applied to the nail bed, hyponychium, and the under surface of the nail plate when it is free of the nail bed (e.g., onycholysis). Contact with the surrounding skin may produce mild, transient irritation (redness).

3. To file and trim nails on a weekly basis during treatment with PENLAC.

4. That removal of the unattached, infected nail, as frequently as monthly, by a health care professional is needed with use of this medication.

5. To inform a health care professional if they have diabetes or problems with numbness in the toes or fingers for consideration of the appropriate nail management program.

6. To inform a health care professional if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing).

7. That up to 48 weeks of daily application with PENLAC and professional removal of the unattached, infected nail, as frequently as monthly, are considered the full treatment needed to achieve a clear or almost clear nail (defined as 10% or less residual nail involvement).

8. That six months of therapy with professional removal of the unattached, infected nail may be required before initial improvement of symptoms is noticed.

9. That a completely clear nail may not be achieved with use of this medication. In clinical studies less than 12% of patients were able to achieve either a completely clear or almost clear toenail.

10. That he/she should not use nail polish or other nail cosmetic products on the treated nails.

11. To not use the medication for any disorder other than that for which it is prescribed.

12. To avoid use near heat or open flame, because product is flammable.

ADVERSE REACTIONS

In the vehicle-controlled clinical trials conducted in the US, 9% (30/327) of patients treated with PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer and 7% (23/328) of patients treated with vehicle reported treatment-emergent adverse events (TEAE) considered by the investigator to be causally related to the test material. With the exception of Skin and Appendages, the incidence of these adverse events, within each body system, was similar between the treatment groups and was less than 1%. For Skin and Appendages, 8% (27/327) and 4% (14/328) of patients in the ciclopirox and vehicle groups, respectively, reported at least one adverse event.

Periungual erythema and erythema of the proximal nail fold were the most common TEAEs causally related to study drug. These events (coded as "rash") were reported in 5% (16/327) of patients treated with PENLAC and 1% (3/328) of patients treated with vehicle.

Other TEAEs thought to be causally related to study material in the US vehicle-controlled studies included nail disorders such as shape change, irritation, ingrown toenail, and discoloration. The incidence of nail disorders was similar between the treatment groups (2% [6/327] in the PENLAC group and 2% [7/328] in the vehicle group).

Application site reactions and/or burning sensation of the skin were considered causally related to study drug in 1% of both PENLAC and vehicle-treated patients (3/327 and 4/328, respectively).

The following table summarizes the most common TEAEs considered causally related to study drug, as reported in the US Phase II/III vehicle-controlled trials.

Body System ***TEAE***	***PENLAC*** ***n (%)***	***Vehicle*** ***n (%)***
No. of Patients Treated	327 (100.00)	328 (100.0)
Patients with Related TEAEs	30 (9.2)	23 (7.0)
Skin and Appendages	27 (8.3)	14 (4.3)
Periungual erythema/erythema of proximal nail fold	16 (4.9)	3 (0.9)
Nail Disorders†	6 (1.8)	7 (2.1)
Application Site Reaction/Burning Sensation	3 (0.9)	4 (1.2)
Other‡	2 (0.6)	0 (0.0)
All other Body Systems	0 - 1 (0.0 - 0.3)	0 - 3 (0 - 0.9)

†Nail disorders such as shape change, irritation, ingrown toenail and discolouration.
‡Other: Dry skin, pruritis.

Use of PENLAC for 48 additional weeks was evaluated in an open-label extension study conducted in patients previously treated in the vehicle-controlled studies. Three percent (9/281) of patients treated with PENLAC experienced at least one TEAE that the investigator thought

was causally related to the test material. Mild rash in the form of periungual erythema (1% [2/281]) and nail disorders (1% [4/281]) were the most frequently reported. The remainder of TEAEs considered causally related to study drug occurred at an incidence of <1%.

In controlled and open-label clinical trials conducted with ciclopirox nail lacquer, 8% outside of the US, adverse events reported were consistent with those seen in the US studies.

Post-Marketing Experience

Contact dermatitis has been reported as an adverse reaction in post-marketing surveillance of ciclopirox-containing products, including ciclopirox nail lacquer, 8%.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The likelihood of overdosage from topical administration of ciclopirox nail lacquer, 8% is extremely low.

In a test of acute oral toxicity in the rat, the LD_{50} was greater than 10 mL/kg of ciclopirox nail lacquer, 8%. This would be equivalent to 600 mL for an adult person weighing 60 kg or more than 1000 vials of 3 mL. Furthermore, overdosage by oral ingestion of nail lacquer would be unlikely because of its unpalatable taste.

DOSAGE AND ADMINISTRATION

PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer should be used as a component of a comprehensive management program for onychomycosis. Removal of the unattached, infected nail - as frequently as monthly - by a health care professional, weekly trimming by the patient, and daily application of the medication are all integral parts of this therapy. Careful consideration of the appropriate nail management program should be given to patients with diabetes (see PRECAUTIONS.)

Nail Care by Health Care Professionals
Removal of the unattached, infected nail - as frequently as monthly- trimming of oncolytic nail and filing of excess horny material should be performed by professionals trained in the treatment of nail disorders.

Nail Care by Patient
Patients should file away (with emery board) loose nail material and trim nails, as required, or as directed by the health care professional, every seven days after PENLAC is removed with isopropyl alcohol.

PENLAC should be applied once daily (preferably at bedtime or eight hours before washing) to all affected nails with the applicator brush provided.

PENLAC should be applied evenly over the entire nail plate.

If possible, PENLAC should be applied to the nail bed, hyponychium, and the under surface of the nail plate when it is free of the nail bed (e.g., onycholysis).

PENLAC should not be removed on a daily basis. Daily applications should be made over the previous coat and removed with isopropyl alcohol every seven days. This cycle should be repeated throughout the duration of therapy.

PHARMACEUTICAL INFORMATION

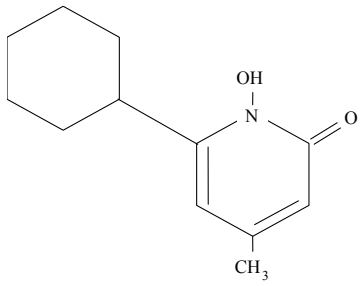
Drug Substance

Common Name: Ciclopirox

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

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

Structural Formula:



Molecular Weight: 207.27 g/mol

Physicochemical Properties

pH: 5.0

pKa: 7.2

Description: Ciclopirox is a white to slightly yellowish white, crystalline powder.

Melting point: 140° – 145°C.

Solubility: It is slightly soluble in water, very soluble in chloroform; freely soluble in dichloromethane and 96% ethanol; soluble in ether.

Composition

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

Stability and Storage Recommendations

PENLAC should be stored at room temperature between 15° and 30° C. To protect from light, replace the bottle into the carton after each use. CAUTION: Flammable. Keep away from heat

and flame.

AVAILABILITY OF DOSAGE FORMS

PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer is a clear, colorless to slightly yellowish solution for topical application to fingernails, toenails and immediately adjacent skin only. It is available in12-gram glass bottle with screw caps which are fitted with brushes.

INFORMATION FOR THE PATIENT

You must receive detailed instructions regarding the use of PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer from your doctor. This product must be used as a part of a treatment program for fungal infections of the nails (onychomycosis) that includes regular removal of the infected nail as well as daily treatment with PENLAC. Discuss your treatment plan with your doctor to plan for regular removal of the loose, infected nail.

Before using this medication, tell your doctor if you:

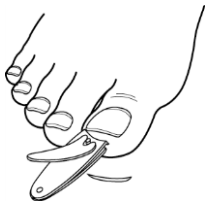
- Are pregnant or breast-feeding a baby
- Are a diabetic who needs insulin injections or has diabetic neuropathy (nerve damage caused by diabetes)
- Have a history of immunosuppression (e.g., are currently taking oral corticosteroids, have repeated or long-lasting shingles (herpes zoster), have oral or genital herpes (herpes simplex))
- Are immunocompromised (e.g., received an organ transplant, or are HIV positive)
- Need medicine to control epilepsy
- Use or require topical corticosteroids every month
- Use steroid inhalers on a regular basis

Patient Information

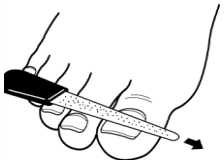
- Use PENLAC in the way that your doctor has told you.
- PENLAC is for **topical use only**.
- If someone accidentally swallows some PENLAC contact your doctor or poison control centre immediately.
- Try not to get PENLAC on any of your skin other than skin right around the treated nail(s). If you get some PENLAC on other parts of your skin, wash it off with soap and water as soon as you can. If it has dried on your skin, you can use a little rubbing alcohol to gently remove it, and then wash with soap and water.
- **Do not use** PENLAC on the eyes or on any mucous membranes (for example, nose, mouth, vagina). Rinse with clear water right away if you do get PENLAC in your eyes or any other mucous membrane.
- Removal of the loose, infected nail, as often as monthly, by your doctor is needed with this product to get the best results. If you have diabetes or problems with numbness in your toes or fingers, talk to your doctor before trimming your nails or removing any nail pieces.
- Tell your doctor if the places where you have applied the product become red, start to itch, burn, blister, swell, or ooze.
- Up to 48 weeks of using PENLAC every day and having your doctor remove the loose, infected nail as often as monthly are usually how long it takes to get a clear or almost clear nail (which means that 10% or less of your nail is still affected). You may need as long as six months of treatment before you first notice your nail(s) getting better.
- Your nail may never become completely clear with this product. In clinical studies less than 12% of patients finished with either a clear or almost clear toenail.
- Do not use nail polish or other nail cosmetic products on the treated nails.
- Avoid use near heat or open flame, because the product is flammable (catches fire easily).

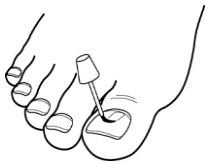
- Use this medication only as told by your doctor or pharmacist. Do not use it for any other reason.

Patient Instructions:



1. Before starting treatment, remove any loose nail or nail pieces using nail clippers or nail files. If you have diabetes or problems with numbness in your toes or fingers, talk to your doctor before trimming your nails or removing any nail pieces.

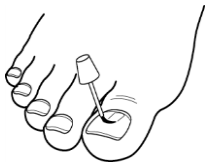




2. Apply PENLAC once daily (bedtime is best) to all affected nails with the applicator brush provided. Apply PENLAC evenly over the entire nail and the skin right around the nail. Where possible, PENLAC should also be put on the bottom side of the nail and the skin beneath it. Let PENLAC dry (about 30 seconds) before putting on socks or stockings. After putting on PENLAC, wait 8 hours before taking a bath or shower.

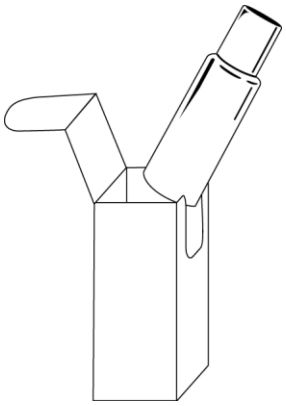
   When you are finished putting PENLAC on your nail(s), put the brush back into the bottle and close the cap tightly. Avoid getting the brush dirty.

3. Apply PENLAC daily over the previous coat.



4. Once a week (every 7 days), remove PENLAC with rubbing alcohol. Remove as much as possible of the damaged nail using scissors, nail clippers, or nail file.

5. Repeat process (steps 2 through 4).



Please Note:

1. To prevent screw cap from sticking to the bottle, do not allow PENLAC to get into the bottle threads.

2. To prevent PENLAC from drying out, the bottle should be closed tightly after every use.

3. To protect from light, replace bottle into carton after each use.

MICROBIOLOGY

Mechanism of Action

The mechanism of action of ciclopirox has been investigated in *in vitro* and *in vivo* studies. 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.

Currently, there is no standardized method for the *in vitro* evaluation of filamentous fungi. Owing to the absence of a standardized testing methodology, results from one study to another can vary substantially.

In vitro/Ex Vivo Studies

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. As a consequence, a broad range of MIC values, 1-20 mcg/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. 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.

PHARMACOLOGY

Clinical Pharmacodynamics

A repeated insult patch study (21-day cumulative irritation) was completed in 205 healthy volunteers to assess the irritation and sensitization potential of topically applied PENLAC (Ciclopirox Topical Solution, 8% w/w) nail lacquer. The study included an induction phase in which subjects were exposed to ciclopirox nail lacquer, 8%, the vehicle base, and petrolatum (negative control) for three weeks and skin reactions were graded; an 11-day rest phase; and a challenge phase of four days to determine if the subject had become sensitized. Neither ciclopirox nail lacquer, 8%, its vehicle base, nor petrolatum led to cumulative irritation indexes suggestive of clinically relevant irritant potential. Thirteen (13), five (5) and one (1) subject showed a grade 1 reaction for ciclopirox nail lacquer, 8%, vehicle, and petrolatum, respectively, at 48 hours post-challenge; none of the reactions met the criteria for a sensitivity response. On the basis of these results it can be expected that ciclopirox nail lacquer, 8% will not lead to frequent irritant reactions or sensitization when used as intended.

Clinical Pharmacokinetics

In Vitro

Radiolabel studies have been conducted with ciclopirox nail lacquer, 8% to determine the *in vitro* penetration and permeation of the active ingredient when the nail lacquer is applied to human excised toenails.

In one study, about 5 mg nail lacquer (equivalent to approximately 400 mcg ciclopirox) was applied to 1 cm^2 of 15 extracted toenails avulsed as a result of onychomycosis. They were of differing thickness with a smooth to scored surface and normal to highly abnormal appearance.

The penetration of ciclopirox up to approximately 0.4 mm nail depth was observed as measured by radioactivity. Nail plate concentrations decreased as a function of nail depth. Nail bed concentrations were not determined.

In Vivo

A single center, open-label study involving patients (n=5) with distal subungual onychomycosis of the fingernails was conducted to determine the systemic absorption of ciclopirox following treatment with PENLAC. The lacquer was applied evenly over the entire nail plate and to the proximal and lateral nail fold areas (approximately 5 mm into the folds) of all fingernails and toenails (i.e., 20 digits). If possible, lacquer also was applied to the nail bed, hyponychium, and the ventral surface of the nail plate when it was free of the nail bed. Before applying a fresh coat, the old coat was removed with soap and water, and each nail was swabbed with isopropyl alcohol.

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.

TOXICOLOGY

Ciclopirox Nail Lacquer, 8%

Acute Toxicity
A single, oral dose of 10 mL/kg body weight of ciclopirox nail lacquer, 8% was administered to 10 male and 10 female Sprague Dawley rats. The oral LD_{50} of ciclopirox nail lacquer, 8% was estimated to be greater than 10 mL/kg for male and female rats. Gross pathological alterations noted in the animal that died included the presence of hardened drug in the stomach and a dark red spot on the urinary bladder. At the Day 7 necropsy, eight of the rats had pea-sized pellets (probably hardened drug-formulation) in their stomachs.

Mutagenicity
The following in vitro genotoxicity tests were conducted with ciclopirox nail lacquer, 8%: Ames Salmonella test (negative); unscheduled DNA synthesis in the rat hepatocytes (negative); cell transformation assay in BALB/c3T3 cell assay (positive). The positive response of the lacquer formulation in the BALB/c3T3 test was attributed to its butyl monoester of poly[methylvinyl ether/maleic acid] resin component (GANTREZ® ES-435), which also tested positive in this test. The cell transformation assay may have been confounded because of the film-forming nature of the resin. GANTREZ® ES-435 tested nonmutagenic in both the in vitro mouse lymphoma forward mutation assay with or without activation and unscheduled DNA synthesis assay in rat hepatocytes.

Carcinogenicity
No carcinogenicity study was conducted with ciclopirox nail lacquer, 8%.

Local Toxicity
Ciclopirox nail lacquer, 8% was tested on the intact and abraded skin of New Zealand White rabbits. Doses of 0.5 mL were applied to two test sites (clipped free of hair, one abraded and one intact) on the flanks of each animal, and the sites were examined for gross signs of skin irritation at 24 and 72 hours post application. There was no edema formation in any animal at either time point. The primary dermal irritation index for this study was 1.17; therefore, ciclopirox nail lacquer, 8% would not be considered a primary irritant.

Ciclopirox nail lacquer, 8% was also tested for primary eye irritation in six New Zealand White rabbits. Signs of eye irritation were observed in the cornea, iris and conjunctivae of all six rabbits at 24, 48 and/or 72 hours post instillation. Slight irritation was noted at 24 hours post instillation in all six rabbits and became increasingly more severe in five of the six rabbits by 72 hours post instillation. Based on the findings seen in this study, ciclopirox nail lacquer, 8% would be considered an eye irritant.

Ciclopirox Active Ingredient

Carcinogenicity
A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dosed topically 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 sites.

Mutagenicity
The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblasts, with and without metabolic activation (positive); gene mutation assay in the HGPRT-test with V79 Chinese hamster lung fibroblasts (negative); unscheduled DNA synthesis in human A549 cells (negative); and BALB/c3T3 cell transformation assay (negative). In an in vivo Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5,000 mg/kg.

Reproduction and Teratology
Oral reproduction studies in rats at doses up to 3.85 mg ciclopirox (as ciclopirox olamine)/kg/day [equivalent to approximately 1.4 times the potential exposure at the maximum recommended human topical dose (MRHTD)] did not reveal any specific effects on fertility or other reproductive parameters. MRHTD (mg/m^2) assumes of 100% systemic absorption of 27.12 mg ciclopirox (~340 mg ciclopirox nail lacquer, 8%) that will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a maximal extent of 50%.

Teratology studies in mice, rats, rabbits, and monkeys at oral doses of up to 77, 23, 23, or 38.5 mg, respectively, of ciclopirox as ciclopirox olamine/kg/day (14, 8, 17, and 28 times MRHTD), or in rats and rabbits receiving topical doses of up to 92.4 and 77 mg/kg/day, respectively (33 and 55 times MRHTD), did not indicate any significant fetal malformations.

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