

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

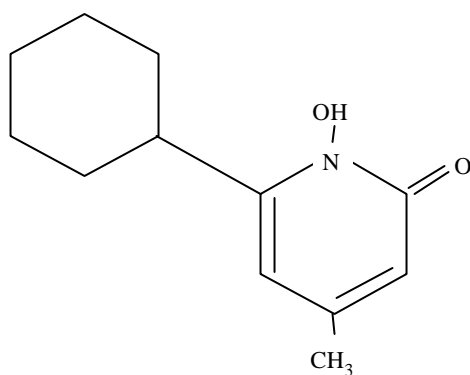
DESCRIPTION

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” ($\leq 10\%$ nail involvement and negative mycology) at the end of study. These results are presented below.

At Week 48 (plus Last Observation Carried Forward) for the Intent-to-Treat (ITT) Population				
	Study 312		Study 313	
	Active	Vehicle	Active	Vehicle
Complete Cure*	6/110 (5.5%)	1/109 (0.9%)	10/118 (8.5%)	0/117 (0%)
Almost Clear**	7/107 (6.5%)	1/108 (0.9%)	14/116 (12%)	1/115 (0.9%)
Negative Mycology Alone***	30/105 (29%)	12/106 (11%)	41/115 (36%)	10/114 (9%)
* Clear nail and negative mycology ** ≤10% nail involvement and negative mycology *** Negative KOH and negative culture				

The summary of reported patient outcomes for the ITT population at 12 weeks following the end of treatment are presented below. Note that post-treatment efficacy assessments were scheduled only for patients who achieved a complete cure.

Post-treatment Week 12 Data for Patients Who Achieved Complete Cure at Week 48				
	Study 312		Study 313	
	Active	Vehicle	Active	Vehicle
Number of Treated Patients	112	111	119	118
Complete Cure at Week 48	6	1	10	0
Post-treatment Week 12 Outcomes:				
Patients Missing All Week 12 Assessments	2	0	2	0
Patients with Week 12 Assessments	4	1	8	0
Complete Cure	3	1	4	0
Almost Clear	2*	1	1*	0
Negative Mycology	3	1	5	0

*Four patients (from studies 312 and 313) who were completely cured did not have post-treatment Week 12 planimetry data.

CONTRAINDICATIONS

PENLAC™ NAIL LACQUER Topical Solution, 8%, is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

PENLAC™ NAIL LACQUER Topical Solution, 8%, is not for ophthalmic, oral, or intravaginal use. For use on nails and immediately adjacent skin only.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of PENLAC™ NAIL LACQUER Topical Solution, 8%, treatment should be discontinued and appropriate therapy instituted.

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.

Information for Patients

Patients should have detailed instructions regarding the use of PENLAC™ NAIL LACQUER Topical Solution, 8%, as a component of a comprehensive management program for onychomycosis in order to achieve maximum benefit with the use of this product.

The patient should be told to:

1. Use PENLAC™ NAIL LACQUER Topical Solution, 8%, as directed by a health care professional. Avoid contact with the eyes and mucous membranes. Contact with skin other than skin immediately surrounding the treated nail(s) should be avoided. PENLAC™ NAIL LACQUER Topical Solution, 8%, is for external use only.
2. PENLAC™ NAIL LACQUER Topical Solution, 8%, should be applied evenly over the entire nail plate and 5 mm of surrounding skin. If possible, PENLAC™ NAIL LACQUER Topical Solution, 8%, 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. Removal of the unattached, infected nail, as frequently as monthly, by a health care professional is needed with use of this medication.
4. Inform a health care professional if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing).
5. Up to 48 weeks of daily applications with PENLAC™ NAIL LACQUER Topical Solution, 8%, 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).

6. Six months of therapy with professional removal of the unattached, infected nail may be required before initial improvement of symptoms is noticed.
7. 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.
8. Do not use the medication for any disorder other than that for which it is prescribed.
9. Do not use nail polish or other nail cosmetic products on the treated nails.
10. Avoid use near heat or open flame, because product is flammable.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No carcinogenicity study was conducted with PENLAC™ NAIL LACQUER Topical Solution, 8%, formulation. 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.

In human systemic tolerability studies following daily application (~340 mg of PENLAC™ NAIL LACQUER Topical Solution, 8%) in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31 ± 28 ng/mL after two months of once daily applications. This level was 159 times lower than the lowest toxic dose and 115 times lower than the highest nontoxic dose in rats and dogs fed 7.7 and 23.1 mg ciclopirox (as ciclopirox olamine)/kg/day.

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.

The following *in vitro* genotoxicity tests were conducted with PENLAC™ NAIL LACQUER Topical Solution, 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.

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/m²) is based on the assumption of 100% systemic absorption of 27.12 mg ciclopirox (~340 mg PENLAC™ NAIL LACQUER Topical Solution, 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%.

Pregnancy:

Teratogenic effects: Pregnancy Category B

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.

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. PENLAC™ NAIL LACQUER Topical Solution, 8%, 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™ NAIL LACQUER Topical Solution, 8%, is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Clinical studies of PENLAC™ NAIL LACQUER Topical Solution, 8%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

ADVERSE REACTIONS

In the vehicle-controlled clinical trials conducted in the US, 9% (30/327) of patients treated with PENLAC™ NAIL LACQUER Topical Solution 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.

The incidence of these adverse events, within each body system, was similar between the treatment groups except for Skin and Appendages: 8% (27/327) and 4% (14/328) of subjects in the ciclopirox and vehicle groups reported at least one adverse event, respectively. The most common were rash-related adverse events: periungual erythema and erythema of the proximal nail fold were reported more frequently in patients treated with PENLAC™ NAIL LACQUER Topical Solution (5% [16/327]) than in patients treated with vehicle (1% [3/328]). Other TEAEs thought to be causally related 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™ NAIL LACQUER Topical Solution group and 2% [7/328] in the vehicle group). Moreover, application site reactions and/or burning of the skin occurred in 1% of patients treated with PENLAC™ NAIL LACQUER Topical Solution (3/327) and vehicle (4/328).

A 21-Day Cumulative Irritancy study was conducted under conditions of semi-occlusion. Mild reactions were seen in 46% of patients with the PENLAC™ NAIL LACQUER Topical Solution, 32% with the vehicle and 2% with the negative control, but all were reactions of mild transient erythema. There was no evidence of allergic contact sensitization for either the PENLAC™ NAIL LACQUER Topical Solution, 8%, or the vehicle base. In the vehicle-controlled studies, one patient treated with PENLAC™ NAIL LACQUER Topical Solution, 8%, discontinued treatment due to a rash, localized to the palm (causal relation to test material undetermined).

Use of PENLAC™ NAIL LACQUER Topical Solution, 8%, 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 subjects treated with PENLAC™ NAIL LACQUER Topical Solution, 8%, 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. Four patients discontinued because of TEAEs. Two of the four had events considered to be related to test material: one patient's great toenail "broke away" and another had an elevated creatine phosphokinase level on Day 1 (after 48 weeks of treatment with vehicle in the previous vehicle-controlled study).

DOSAGE AND ADMINISTRATION

PENLAC™ NAIL LACQUER Topical Solution, 8%, 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.

Nail Care By Health Care Professionals:

Removal of the unattached, infected nail, as frequently as monthly, trimming of onycholytic nail, and filing of excess horny material should be performed by professionals trained in treatment of nail disorders.

Nail Care By Patient:

Patients should file away (with emery board) loose nail material and trim nails, as required, every seven days after PENLAC™ NAIL LACQUER Topical Solution, 8%, is removed with alcohol.

PENLAC™ NAIL LACQUER Topical Solution, 8%, should be applied once daily (preferably at bedtime or eight hours before washing) to all affected nails with the applicator brush provided. The PENLAC™ NAIL LACQUER Topical Solution, 8%, should be applied evenly over the entire nail plate.

If possible, PENLAC™ NAIL LACQUER Topical Solution, 8%, 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).

The PENLAC™ NAIL LACQUER Topical Solution, 8%, should not be removed on a daily basis. Daily applications should be made over the previous coat and removed with alcohol every seven days. This cycle should be repeated throughout the duration of therapy.

HOW SUPPLIED

PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is supplied in 3.3 mL (NDC 0088-2200-13) glass bottles with screw caps which are fitted with brushes.

Protect from light (e.g., store the bottle in the carton after every use).

PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be stored at room temperature between 59° and 86° F (15° and 30° C).

CAUTION: Flammable. Keep away from heat and flame.

Rx ONLY

References:

1. Dittmar W., Lohaus G. 1973. HOE296, A new antimycotic compound with a broad antimicrobial spectrum. *Arzneim-Forsch./Drug Res.* 23:670-674.

2. Niewerth *et. al.*, 1998. Antimicrobial susceptibility testing of dermatophytes: Comparison of the agar macrodilution and broth micro dilution tests. *Chemotherapy*. 44:31-35.
3. Yang *et. al.* 1997. A new simulation model for studying in vitro topical penetration of antifungal drugs into hard keratin. *J. Mycol. Med.* 7:195-98.



**PENLAC™ NAIL LACQUER (ciclopirox)
Topical Solution, 8%**

Patient Information and Instructions

Patients should have detailed instructions regarding the use of PENLAC™ NAIL LACQUER Topical Solution, 8%, as a component of a comprehensive management program for onychomycosis in order to achieve maximum benefit with the use of this product. Discuss your treatment plan with your health care professional for regular removal of the unattached, infected nail.

Before using this medication, tell your doctor if you:

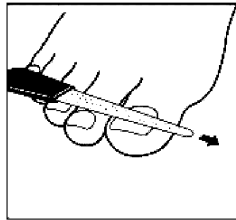
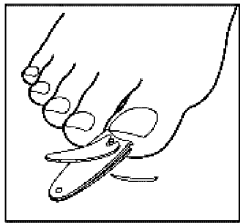
- Are pregnant or nursing
- Are an insulin dependent diabetic or have diabetic neuropathy
- Have a history of immunosuppression
- Are immunocompromised (e.g., received an organ transplant, etc.)
- Require medication to control epilepsy
- Use or require topical corticosteroids on a repeated monthly basis
- Use steroid inhalers on a regular basis

Patient Information:

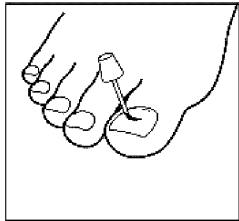
- Use PENLAC™ NAIL LACQUER Topical Solution, 8%, as directed by your health care professional.
- PENLAC™ NAIL LACQUER Topical Solution, 8%, is for external use only.
- Contact with skin other than skin immediately surrounding the treated nail(s) should be avoided.
- Avoid contact with the eyes and mucous membranes.
- Removal of the unattached, infected nail, as frequently as monthly, by your health care professional is needed with use of this medication to obtain maximal benefit with use of this product.
- Inform your health care professional if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing).

- Up to 48 weeks of daily applications with PENLAC™ NAIL LACQUER Topical Solution, 8%, and professional removal, as frequently as monthly, of the unattached, infected nail are considered the full treatment time to achieve a clear or almost clear nail (defined as 10% or less residual nail involvement). Six months of therapy with professional removal of the unattached, infected nail may be required before initial improvement of symptoms is noticed.
- 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 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 product is flammable.

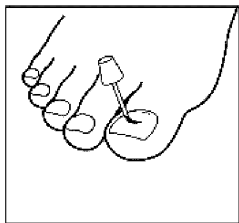
Patient Instructions



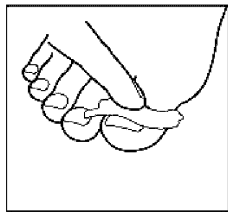
1. Before starting treatment, remove any loose nail or nail material using nail clippers or nail files.



2. Apply PENLAC™ NAIL LACQUER Topical Solution, 8%, once daily (preferably at bedtime) to all affected nails with the applicator brush provided. Apply the lacquer evenly over the entire nail. Where possible, nail lacquer should also be applied to the underside of the nail and to the skin beneath it. Allow lacquer to dry (approximately 30 seconds) before putting on socks or stockings. After applying medication, wait 8 hours before taking a bath or shower.



3. Apply PENLAC™ NAIL LACQUER Topical Solution, 8%, daily over the previous coat.



4. Once a week, remove the PENLACT™ NAIL LACQUER Topical Solution, 8%, with alcohol. Remove as much as possible of the damaged nail using nail clippers, or nail files.
5. Repeat process (steps 2 through 4).

Please Note:



1. To prevent screw cap from sticking to the bottle, do not allow solution to get into the bottle threads.
2. To prevent the solution from drying out, bottle should be closed tightly after every use.
3. To protect from light, replace bottle into carton after each use.

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Prescribing Information as of December 1999