Ciclopirox Treatment Kit
Ciclopirox Topical Solution, 8% (Nail Lacquer)
Topical Toen Freshener

For use on fingernails and toenails and immediately adjacent skin only. Not for use in eyes.

DESCRIPTION
Ciclopirox Topical Solution, 8% (Nail Lacquer) contains a synthetic antifungal agent, ciclopirox. It is intended for topical use on fingernails and toenails and immediately adjacent skin.

Each gram of Ciclopirox Topical Solution, 8% (Nail Lacquer) contains 80 mg ciclopirox in a solution base consisting of ethyl alcohol, NF, isopropyl alcohol, USP, and 5 mg monosodium phosphate (as sodium dihydrogen phosphate). Ethyl alcohol and isopropyl alcohol are solvents that vaporize after application.

Ciclopirox Topical Solution, 8% (Nail Lacquer) is a clear, colorless to slightly yellowish solution.

The chemical name for ciclopirox is 6-ethylcyclopentyl-1-hydroxy-4-methyl-2(1H)-pyridine, with the molecular formula C12H13NO and a molecular weight of 202.27. The CAS Registry Number is 29342-80-9. The chemical structure is

INDICATIONS AND USAGE
(If you are not using the printed copy of this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

Ciclopirox Topical Solution, 8% (Nail Lacquer) as a component of a comprehensive management program, is indicated as topical treatment in immunocompetent patients with tinea pedis with involvement of the sole and adjacent skin. Tinea pedis without involvement, due to Trichophyton rubrum. The comprehensive management program includes: the removal of the unattached, infected nail as frequently as possible, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures.

No data have been obtained 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. Ciclopirox Topical Solution, 8% (Nail Lacquer) should be used only under medical supervision as described above.

The effectiveness and safety of Ciclopirox Topical Solution, 8% (Nail Lacquer) in the following populations has not been studied. The clinical trials with use of Ciclopirox Topical Solution, 8% (Nail Lacquer) 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, miliar or recurrent 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) type feet were also excluded.

The safety and efficacy of using Ciclopirox Topical Solution, 8% (Nail Lacquer) daily for greater than 48 weeks has not been established.

Clinical Trial Data
The reported patient outcomes for Ciclopirox Topical Solution, 8% (Nail Lacquer) in treatment of onychomycosis of the toenails 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% (Nail Lacquer) in conjunction with monthly removal of the unattached, infected nail by the investigator. Ciclopirox Topical Solution, 8% (Nail Lacquer) was applied for 48 weeks. In one study, patients had 20-65% involvement of the great target toenail. Statistical significance was demonstrated in one of two studies for the endpoint "complete cure" (clear nail and negative mycology) at week 48. After 48 weeks, ciclopirox showed 15% (28/184) complete cure involving and negative mycology at the end of study. These results are presented below.

**At Week 48 (plos Last Observation Carried Forward) for the Intent-to-Treat (IT) Population**

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<thead>
<tr>
<th>Study</th>
<th>Active</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>Study 315</td>
<td>1/3 (3%)</td>
<td>0/3 (0%)</td>
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<tr>
<td>Study 312</td>
<td>1/1 (1%)</td>
<td>0/1 (0%)</td>
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<tr>
<th>Clear Nail and Negative Mycology</th>
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<tr>
<td>Study 312: 2/11 (20%); Study 315: 1/11 (9%)</td>
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<tr>
<th>Negative Mycology</th>
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<td>Study 312: 12/10 (12%); Study 315: 1/10 (10%)</td>
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* Clear nail and negative mycology
* Negative mycology

The summary of reported patient outcomes for the ITT population at 12 weeks following removal of the unattached, infected nail after ciclopiroz treatment are presented below. No further 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

<table>
<thead>
<tr>
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<th>Complete Cure</th>
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* Four patients (from studies 312 and 315) who were completely cured did not have post-treatment Week 12 plasma levels.

CONTRAINdications
Ciclopirox Topical Solution, 8% (Nail Lacquer) is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS
Do not use ciclopirox Topical Solution, 8% (Nail Lacquer) for any disorder other than that for which it is prescribed.

Geriatric Use:
Based on the safety profile in adults, Ciclopirox Topical Solution, 8% (Nail Lacquer) will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a maximal extent of 50%.

Pediatric Use:
Based on the safety profile in adults, Ciclopirox Topical Solution, 8% (Nail Lacquer) is considered safe for use in children two years and older. No clinical trials have been conducted in the pediatric population.

Carcinogenicity, Mutagenicity, Impairment of Fertility:
No carcinogenicity study was conducted with Ciclopirox Topical Solution, 8% (Nail Lacquer). Various in vitro/in vivo mutagenicity assays were conducted with ciclopiroz (1% and 5% solutions in polyethylene glycol 400) in female mice dosed topicaly twice per week for 50 weeks followed by a 6-month drug-free observation period to necropsy revealed no evidence of tumors at the application sites.

Drug Interactions
The following list of drug interactions is not intended to be all inclusive. Use of ciclopiroz with other drugs is not recommended. Drug Interactions have shown that ciclopiroz is rapidly absorbed after oral administration and completely eliminated in all species via liver and kidneys. Most of the compound is excreted either unaltered or as glucuronide. Oral administration of 10 mg of radio labeled drug (14C-ciclopiroz) to healthy volunteers, approximately 96% of the radioactivity was excreted directly after oral dosing. Ninety percent of the fourthly excreted radioactivity was in the form of glucuronides. Thus, glucuronidation is the main metabolic pathway of this compound.

Systemic absorption of ciclopiroz was determined in 5 patients with dermatophytosis onychomycoses, after application of Ciclopiroz Topical Solution, 8% (Nail Lacquer) to 20 digits and adjacent 5 mm of skin once daily for 6 months. Rand onychomycoses, after application of ciclopiroz Topical Solution, 8% (Nail Lacquer) was studied in 119 patients. About 10% of the radioactivity was eliminated in the urine of these patients. About 20% of the radioactivity was eliminated in the feces as ciclopiroz glucuronide. After oral administration of 10 mg of radio labeled ciclopiroz there was 40% of the radioactivity eliminated in the urine and 20% was excreted in the feces.

Ciclopiroz Topical Solution, 8% (Nail Lacquer) is considered safe for use with other topical antifungal agents. The use of ciclopiroz with other drugs is not recommended. Drug Interactions have shown that ciclopiroz is rapidly absorbed after oral administration and completely eliminated in all species via liver and kidneys. Most of the compound is excreted either unaltered or as glucuronide. Oral administration of 10 mg of radio labeled drug (14C-ciclopiroz) to healthy volunteers, approximately 96% of the radioactivity was excreted directly after oral dosing. Ninety percent of the fourthly excreted radioactivity was in the form of glucuronides. Thus, glucuronidation is the main metabolic pathway of this compound.

Studies conducted in the US, 9% (3027) of patients treated with Ciclopirox Topical Solution, 8% (Nail Lacquer) and 7% (2298) of patients treated with vehicle control solution showed adverse events (AE) considered by the investigator to be causally related to the test article. The incidence of these adverse events, within each body system, was similar between the treatment groups and placebo group. The most common AE that occurred in 4% (134/3027) of subjects in the ciclopiroz and vehicle groups reported at least one adverse event, respectively. The most common were nail-related adverse events: paronychia erythema and edema of the nail fold and infection in patients treated with Ciclopirox Topical Solution, 8% (Nail Lacquer) (5% [163/327]) than in patients treated with vehicle (1% [33/327]). Other AE was thought to be causally related nail disorders. No change in shape change, irritation, infection and burning were reported. The incidence of nail disorders was similar between the treatment groups (2% [62/327] in the Ciclopiroz Topical Solution, 8% (Nail Lacquer) group and 2% [63/327] in the vehicle group). Moreover, application site reactions similar to Onychomycosis occurring in 1% of patients treated with Ciclopiroz Topical Solution, 8% (Nail Lacquer) (33/327) and vehicle (4/327).

CLINICAL PHARMACOLOGY
Mechanism of Action
The mechanism of action of ciclopiroz has been investigated using various in vitro and in vivo infection models. One in vitro study suggested that ciclopiroz acts by chelation of polyvalent cations (Fe3+ or Al3+) 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.

Activities in vivo and in vitro
Ciclopiroz is highly effective against various broth or solid media with and without additional nutrients have been utilized to determine ciclopiroz minimal inhibitory concentration (MIC) values for the dermatophytes. As expected, nail plate concentrations decreased as a function of nail depth.

The penetration of the that eleven of these 24 patients took concomitant medication containing ciclopiroz.
A 21-Day Cumulative Irritancy study was conducted under conditions of semi-
occlusion. Mild reactions were seen in 4% of patients with the Ciclopirox Topical
Solution, 8% (Nail Lacquer), 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 Ciclopirox Topical Solution, 8% (Nail Lacquer), or
the vehicle base. In a separate study of the photosensitization potential of Ciclopirox
Topical Solution, 8% (Nail Lacquer) in a maximized test design that included the
occluded application of sodium lauryl sulfate, no photoallergic reactions were
noted. In four subjects localized allergic contact reactions were observed. In the vehicle-
controlled studies, one patient treated with Ciclopirox Topical Solution, 8% (Nail
Lacquer) discontinued treatment due to a rash, localized to the palm (causal relation to
test material undetermined).
Use of Ciclopirox Topical Solution, 8% (Nail Lacquer) 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
Ciclopirox Topical Solution, 8% (Nail Lacquer) 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).

DOSEAGE AND ADMINISTRATION
Ciclopirox Topical Solution, 8% (Nail Lacquer) should be used as a component of a
comprehensive management program for onychomycosis. Removal of the unattached,
injected 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 Professional:
Removal of the unattached, injected 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, or as directed by the health care professional, every seven days after
Ciclopirox Topical Solution, 8% (Nail Lacquer) is removed with alcohol. Ciclopirox
Topical Solution, 8% (Nail Lacquer) should be applied once daily (preferably at
bedtime or eight hours before washing) to all affected nails with the applicator brush
designed to provide. Ciclopirox Topical Solution, 8% (Nail Lacquer) should be applied evenly
over the entire nail plate.
If possible, Ciclopirox Topical Solution, 8% (Nail Lacquer) 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., onycholyis). Ciclopirox Topical Solution, 8% (Nail Lacquer) 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
Ciclopirox Treatment Kit NDC (42192-714-01) contains 1 – 6.6 ml bottle of
Ciclopirox Topical Solution, 8% (Nail Lacquer) (glass bottle with screw cap which is
fitted with a brush), 1 – 28 ml bottle Topical Toe Freshener.

Protect from light (e.g., store the bottle in the carton after every use).
Ciclopirox Topical Solution, 8% (Nail Lacquer) 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

Information for Patients:
Patients should have detailed instruction regarding the use of Ciclopirox Topical
Solution, 8% (Nail Lacquer) 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 Ciclopirox Topical Solution, 8% (Nail Lacquer) as directed by a health care
professional. Avoid contact with eyes and mucous membranes. Contact with skin
other than skin immediately surrounding the treated nail(s) should be avoided.
Ciclopirox Topical Solution, 8% (Nail Lacquer) is for external use only.
2. Ciclopirox Topical Solution, 8% (Nail Lacquer) should be applied evenly over the
entire nail plate and 5 mm of surrounding skin. If possible, Ciclopirox Topical
Solution, 8% (Nail Lacquer) 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., onycholyis).
Contact with the surrounding skin may produce mild, transient irritation
(redness).
3. Removal of the unattached, injected nail, as frequently as monthly, by a health care
professional is needed with the use of this medication. Inform a health care
professional if you have diabetes or problems with numbness in your toes or fingers
for consideration of the appropriate nail management program.
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 Ciclopirox Topical Solution, 8%
(Nail Lacquer) and professional removal of the unattached, injected 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, injected 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 15% 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.

REFERENCES:
-Niewerth et al., 1998. Antimicrobial susceptibility testing of dermatophytes:
Comparison of the agar macrodilution and broth micro dilution tests. Chemotherapy.
44:31-35.

Ganvil is a registered trademark of GAF Corporation.

MANUFACTURED FOR:
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