CNL8 - ciclopirox solution
Innocutis Holdings LLC

CNL8 (ciclopirox topical solution 8%)Nail Lacquer

DESCRIPTION

CNL8 (ciclopirox topical solution, 8%) nail lacquer.

For use on fingernails and toenails and immediately adjacent skin only.

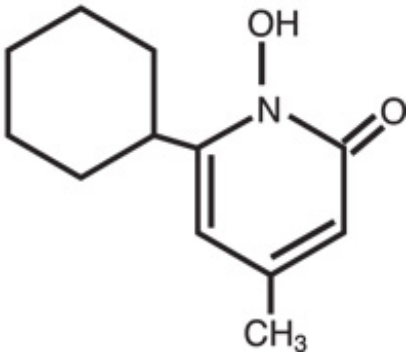
Not for use in eyes.

CNL8 (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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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.

CNL8 (ciclopirox topical solution, 8%) nail lacquer is a clear, colorless to slightly yellowish solution.

The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, with the molecular formula C12H17NO2 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 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.(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 for 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 crossresistance to ciclopirox and other known antifungal agents have not been performed.

Antifungal Drug Interaction: 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 (14Cciclopirox) 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 CNL8 (ciclopirox topical solution, 8%) 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 less than 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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 & USAGE

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

CNL8 (ciclopirox topical solution,8%) nail lacquer 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 Tricho-phyto 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.

CNL8 (ciclopirox topical solution, 8%) nail lacquer should be used only under medical supervision as described above.

The effectiveness and safety of CNL8 (ciclopirox topical solution, 8%) nail lacquer in the following populations have not been studied. The clinical trials with use of CNL8 (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 derma-tomycoses, 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer daily for greater than 48 weeks have not been established.

CLINICAL STUDIES

The results of use of CNL8 (ciclopirox topical solution, 8%) nail lacquer 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer in conjunction with monthly removal of the unattached, infected toenail by the investigator. CNL8 (ciclopirox topical solution, 8%) nail lacquer 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.
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%)
Negative Mycology Alone ***	30/105 (29%)	12/106 (11%)	41/115 (36%)	10/114 (9%)

*Clear nail and negative Mycology
** Less than or equal to 10% nail involvement and negative mycology

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
Completed Cure at Week 48	6	1	10	1
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

CNL8 (ciclopirox topical solution, 8%) nail lacquer is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

CNL8 (ciclopirox topical solution, 8%) nail lacquer 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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 instruction regarding the use of CNL8 (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 CNL8 (ciclopirox topical solution, 8%) nail lacquer as directed by a health care professional. Avoid contact witheyes and mucous membranes. Contact with skin other than skin immediately surrounding the treated nail(s) should be avoided. CNL8 (ciclopirox topical solution, 8%) nail lacquer is for external use only.

2.CNL8 (ciclopirox topical solution, 8%) nail lacquer should be applied evenly over the entire nail plate and 5 mm of surrounding skin. If possible, CNL8 (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., 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 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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. Do not use nail polish or other nail cosmetic products on the treated nails.

9. Avoid use near heat or open flame, because product is flammable.

CARCINOGENESIS, MUTAGENESIS and IMPAIRMENT OF FERTILITY

No carcinogenicity study was conducted with CNL8 (ciclopirox topical solution, 8%) nail lacquer 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer) 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 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.
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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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. CNL8 (ciclopirox topical solution, 8%) nail lacquer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MONTHERS
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 CNL8
(ciclopirox topical solution, 8%) nail lacquer is administered to a nursing woman.

PEDIATRIC USE
Based on the safety profile in adults, CNL8 (ciclopirox topical solution, 8%) nail lacquer is considered safe for use in children twelve years and older. No clinical trials have been conducted in the pediatric population.

GERIATRIC USE
Based on the safety profile in adults, CNL8 (ciclopirox topical solution, 8%) nail lacquer is considered safe for use in children twelve years and older. No clinical trials have been conducted in the pediatric population.

ADVERSE REATIONS

In the vehicle-controlled clinical trials conducted in the US, 9% (30/327) of patients treated with CNL8 (ciclopirox topical solution, 8%) 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. 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer (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 CNL8

(ciclopirox topical solution, 8%) nail lacquer group and 2% [7/328] in the vehicle group). Moreover, application site reactions and/or burning of the skin occurred in 1% of patients in 1% of patients treated with CNL8 (ciclopirox topical solution, 8%) nail lacquer (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 CNL8 (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 CNL8 (ciclopirox topical solution, 8%) nail lacquer or the vehicle base. In a separate study of the photosensitization potential of CNL8 (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 CNL8 (ciclopirox topical solution, 8%) nail lacquer discontinued treatment due to a rash, localized to the palm (causal relation to test material undetermined).

Use of CNL8 (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. Threecpercent (9/281) of subjects treated with CNL8 (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).

To report SUSPECTED ADVERSE REACTIONS contact JSJ Pharmaceuticals at 800-499-4468.

DOSAGE and ADMINISTRATION

CNL8 (ciclopirox topical solution, 8%) 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 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer is removed with alcohol. CNL8 (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 provided. CNL8 (ciclopirox topical solution, 8%) nail lacquer should be applied evenly over the entire nail plate.

If possible, CNL8 (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., onycholysis).

CNL8 (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

CNL8 nail kit (ciclopirox topical solution, 8%), Swabplus nail lacquer remover, emery board – which contains 3 - 5 ml bottles of CNL8 (ciclopirox topical solution, 8%) nail lacquer (glass bottles with screw caps which are fitted with brushes), 25 - 0.15 ml nail lacquer remover swabs and 1 emery board (NDC 68712-027-01).

CNL8 (ciclopirox topical solution, 8%) nail lacquer, single count 5 ml bottle (NDC 68712-027-03).

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

CNL8 (ciclopirox topical solution, 8%) nail lacquer should be stored at room temperature between 59° and 86° F (15° and 30° C).

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3. Removal of the unattached, infected 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 CNL8 (ciclopirox topical solution, 8%) nail lacquer 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.

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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 productson the treated nails.

10. Avoid use near heat or open flame, because product is flammable.

Manufactured for:

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1-800-499-4468
CNL8nails.com

REFERENCES

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 antifungaldrugs into hard keratin. J. Mycol. Med. 7:195-98. Gantrez is a registered trademark of GAF Corporation

Rev. 419:00 12/07

CNL8
ciclopirox solution

Product Information			

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68712-027
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CICLOPIROX (UNII: 19W019ZDRJ) (CICLOPIROX - UNII:19W019ZDRJ)	CICLOPIROX	2.28 g in 1 mL

Inactive Ingredients

Ingredient Name	Strength
ETHYL ACETATE (UNII: 76845O8NMZ)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68712-027-01	3 in 1 CARTON		
1	NDC:68712-027-03	5 mL in 1 BOTTLE, GLASS		
2	NDC:68712-027-03	5 mL in 1 BOTTLE, GLASS		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078270	10/31/2008	

Labeler - Innocutis Holdings LLC (071501252)

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