DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-022/S-004

Dermik Labroatories
Attn: Gary Feiss, M.S.
Head, Clinical Development, Regulatory Affairs/Compliance
1050 Westlakes Drive
Berwyn, PA 19312

Dear Mr. Feiss:

Please refer to your supplemental new drug application dated June 4, 2004, received June 7, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Penlac® Nail Lacquer (ciclopirox) Topical Solution, 8%.

We acknowledge receipt of your submission dated August 10, August 16 and December 1 (facsimile), 2004.

This supplemental new drug application provide for revised labeling to reflect the final study results for contact sensitization.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Division Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
12/3/04 03:12:26 PM
sign off for Dr. Jonathan Wilkin, Division Director

Penlac® Nail Lacquer
(ciclopirox) Topical Solution, 8%

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

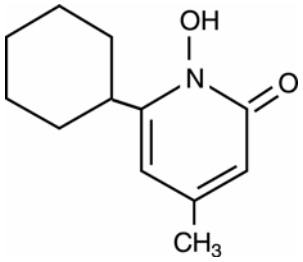
DESCRIPTION

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)-pyridone, 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

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