PRODUCT INFORMATION
RejuveNail® Anti-fungal Nail Lacquer

NAME OF THE MEDICINE

Generic name: Ciclopirox
Chemical name: 6-cyclohexyl-1-hydroxy-4-methyl-2-(1H) pyridine
Molecular formula: C_{12}H_{17}NO_{2}  MW: 207.3
CAS number: 29342-05-0
Chemical structure:

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\begin{align*}
&\text{CH}_3 \\
&\text{OH} \\
&\text{N} \\
&\text{O} \\
&\text{C}_6\text{H}_{15}\text{N}\text{O}_2
\end{align*}
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DESCRIPTION

Ciclopirox is a white to slightly yellowish-white, crystalline powder which is odourless to almost odourless. It is freely soluble in dichloromethane and ethanol 96%, very soluble in chloroform, soluble in ether and slightly soluble in water. The pKa value is 7.2.

Composition
Active: Ciclopirox 80mg/g (8% w/w).
Inactives: Ethyl acetate, ethanol, cetostearyl alcohol, hydroxypropyl chitosan and purified water.

The excipients ethyl acetate and ethanol are solvents that vaporise after application.
RejuveNail Anti-fungal Nail Lacquer is a clear, colourless to slightly yellow solution.

PHARMACOLOGY

Ciclopirox is a broad spectrum antimycotic with a high penetrating power. It has a fungicidal effect on dermatophytes, yeasts, moulds and other fungi.

Ciclopirox is the free acid of ciclopiroxolamine. Ciclopirox has an identical spectrum of activity to ciclopiroxolamine. Ciclopirox is a hydroxypyridone derivative that is structurally unrelated to the imidazole derivatives or other antifungals.

Ciclopirox has several mechanisms of action including chelation of polyvalent metal cations (e.g. Fe^{3+} and Al^{3+}). It thus inhibits the metal-dependent enzymes, including those responsible for the degradation of peroxides within fungal cells.
The MIC of ciclopirox for 34 of 35 fungal and yeast strains: dermatophytes (Trichophyton species, Microsporum species, Epidermophyton species), yeasts (Candida albicans, other Candida species) were between 0.98–3.9μg/mL (in vitro). For Trichophyton mentagrophytes, the MIC was 7.8μg/mL. Ciclopirox has also been shown in vitro to be active against a number of gram positive and gram negative pathogenic bacteria (e.g. Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, relevant Staphylococcus and Streptococcus species) and Mycoplasma species, Trichomonas vaginalis and Actinomyces. Most of the strains tested were in the range of 7.7 to 31.3μg/mL.

In more than 2 decades no case of resistance to ciclopirox has ever been reported.

Table of susceptibility (strains relevant to illness)

<table>
<thead>
<tr>
<th>Dermatophytes</th>
<th>Trichophyton rubrum</th>
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<tbody>
<tr>
<td></td>
<td>Trichophyton mentagrophytes</td>
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<tr>
<td></td>
<td>Trichophyton spp</td>
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<tr>
<td></td>
<td>Microsporum canis</td>
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<td></td>
<td>Epidermophyton floccosum</td>
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<td>Yeasts</td>
<td>Candida albicans</td>
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<td></td>
<td>Candida parapsilosis</td>
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<tr>
<td>Moulds</td>
<td>Scopulariopsis brevicaulis</td>
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<tr>
<td></td>
<td>Aspergillum spp</td>
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<tr>
<td></td>
<td>Fusarium solani</td>
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RejuveNail Anti-fungal Nail Lacquer has been developed for the treatment of fungal infections of the nails. The active ingredient ciclopirox is formulated in patented technology (ONY-TEC) for delivery of the active to nails. It is a hydro-alcoholic solution of hydroxypropyl chitosan, which has the following properties: good solubility in water, high plasticity, affinity to keratin, wound healing activity and high compatibility with human tissues.

After application on the nail surface, RejuveNail Anti-fungal nail lacquer forms an invisible film, permeable to moisture and air, which adheres to the keratin structure of the nail allowing immediate release and good penetration of the active ingredient to the nail substrate. By achieving fungicidal concentrations at the site of infection, the active substance leads to irreversible binding to the fungal cell wall and this causes inhibition of the uptake of components needed for cellular synthesis and of the respiratory chain.

Pharmacokinetics

Absorption: A very small amount of ciclopirox is absorbed systemically (<2% of the applied dose and the blood levels in a long term study were 0.904ng/ml (n=163) and 1.144ng/ml (n=149) after 6 and 12 months of treatment, respectively. This shows that the drug exerts its activity particularly at the local level and the risk of possible interference with the normal body functions is negligible.

Distribution: Ciclopirox nail lacquer penetrates the nail plate via a transungal delivery system. When the solvent evaporates the concentration of ciclopirox increases, providing a concentration gradient that facilitates the transfer of the drug through the nail plate. This mode of application permits the distribution of the active compound throughout the entire nail plate, including the lateral margins and the onycholytic portions of the nail.

Metabolism: Glucuronidation is the main metabolic pathway for ciclopirox.

Excretion: Excreted renally in the form of glucuronides within 12 hours of oral administration.
CLINICAL TRIALS

RejuveNail Anti-fungal nail lacquer has been investigated in a long term clinical study in 467 patients with onychomycosis. In a three arm study versus placebo (RejuveNail Anti-fungal vehicle) and a commercially available formulation of ciclopirox 8% nail lacquer (Penlac®). All treatments were applied every day for 48 weeks to the infected nails. The patients were followed up for a further period of 12 weeks. As required by the different characteristics of the formulations, reference ciclopirox nail lacquer was removed once a week by means of solvents and nail filing, while RejuveNail Anti-fungal and placebo (both water-soluble) simply by washing.

The statistical design was superiority to placebo and non-inferiority to the reference product.

Efficacy data were available in 454 patients (ITT) and confirmed in 433 patients (PP). RejuveNail Anti-fungal nail lacquer met the primary endpoint, being significantly superior to placebo and non-inferior to reference ciclopirox. The effect was evidenced on the primary endpoint “cure” rate (namely patients with negative mycology and 100% complete clear nail) and on the secondary endpoint “responder” rate (patients with negative mycology and ≥ 90% clear nail).

At the endpoint the percentages of ITT patients with complete cure in the RejuveNail Anti-fungal group (5.7%) were higher than in the reference group (3.2%), compared with 0% for the placebo group. Similarly, the responder rate for RejuveNail (24%) was higher than the reference group (17.3%) and significantly superior to placebo (6.4%).

At week 60, i.e. 12 weeks after end of treatment, percentages of patients with complete cure (12.7%) and of responders (28.7%), in the RejuveNail Anti-fungal group, further increased compared to the reference group (5.8% and 17.3% respectively), being 119% higher for cure rate (statistically significant, p<0.05) and 66% higher for responder rate (statistically significant, p<0.05); in addition to being significantly superior to placebo (1.3% and 14.7% respectively). RejuveNail Anti-fungal nail lacquer showed a continuous increase in both efficacy endpoints during weeks 48, 52 and 60, differently from the reference product.

Furthermore, microbiological culture demonstrated eradication of the causative pathogen in over 90% of patients within 24 weeks of treatment with both, test and reference products. Microbiological culture remained negative in almost 80% of patients at the end of follow-up.

INDICATIONS

For the treatment of fungal nail infections. For the treatment of onychomycoses caused by dermatophytes, yeasts and moulds.

CONTRAINDICATIONS

Hypersensitivity to ciclopirox or any of the ingredients in the lacquer.

RejuveNail Anti-fungal nail lacquer should not be used in pregnancy or lactation.

Not recommended for use in children or adolescents below 18 years of age as there is insufficient experience in this age group.

PRECAUTIONS

RejuveNail Anti-fungal nail lacquer is not for ophthalmic, oral or intravaginal use. RejuveNail Anti-fungal Nail Lacquer is known to be an eye irritant. Care should be taken to ensure the patient does not inadvertently transfer RejuveNail Anti-fungal nail lacquer to the eyes by touching them after applying the lacquer to their fingernails.
If a reaction suggesting sensitivity or chemical irritation should occur with the use of RejuveNail Anti-fungal nail lacquer, treatment should be discontinued and appropriate therapy instituted.

Effects on Fertility

At the oral dosage of 5mg/kg, a reduced fertility index in the rat was observed.

Use in pregnancy

Pregnancy Category B3.

There are no clinical data on exposed pregnant women for ciclopirox. In animal studies, no foetal malformations due to ciclopirox were observed in mouse, rat, rabbit and monkey studies by oral, subcutaneous or dermal dosing. Delayed ossification was observed in mice and rats receiving oral or subcutaneous doses of ciclopirox, but not in rats or rabbits by dermal application.

RejuveNail Anti-fungal Nail Lacquer should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

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 RejuveNail Anti-fungal Nail Lacquer is administered to a nursing woman.

Paediatric use

Safety and effectiveness in children below the age of 18 years have not been established, therefore, RejuveNail Anti-fungal Nail Lacquer is not recommended for use in children.

Use in the elderly

In clinical studies, no overall differences in safety were observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Genotoxicity

Ciclopirox did not cause gene mutation in bacteria gene mutation assays or in the HGPRT-test with V79 Chinese hamster cells. Nor did it cause chromosome aberrations in V79 Chinese cells in vitro or in an in vivo Chinese hamster bone marrow cytogenetic assay or cause DNA damage in the unscheduled DNA synthesis assay in A549 human cells.

Carcinogenicity

Limited information on the carcinogenicity of ciclopirox is available. Ciclopirox (1 and 5% solution in polyethylene glycol 400) did not induce tumours at the treated site in female mice dosed topically twice per week for 50 weeks followed by a 6 month observation period.

INTERACTIONS WITH OTHER MEDICINES

Nil known.

ADVERSE EFFECTS

RejuveNail Anti-fungal Nail Lacquer is generally well tolerated. Where RejuveNail Anti-fungal Nail Lacquer has come into contact with skin adjacent to the nail, a light reddening or scaling of the skin has been observed in a few exceptional cases.

In the long term, three arm study versus placebo (RejuveNail Anti-fungal vehicle) and a commercially available formulation of ciclopirox 8% nail lacquer (Penlac®), tolerability at the application site was continuously monitored throughout the treatment period. Elicited signs/symptoms were recorded in a minority of patients in all treatment groups. Overall,
signs or symptoms were more frequent with the reference ciclopirox product (8.6% signs and 16% symptoms) than with RejuveNail Anti-fungal (2.8% signs and 7.8% symptoms). In placebo group, 7.2% signs and 12.4% symptoms were recorded. The most frequent sign recorded was erythema. This was observed by the investigator in 2.8% of patients in RejuveNail Anti-fungal group, and in 8.6% in reference group. Erythema was additionally reported by a further 2.1% of patients in the reference group. The most frequent symptom was burning. This was reported in 2.8% of patients in RejuveNail Anti-fungal group and in 10.7% in reference group.

For the frequency of occurrence of side effects, the following phrases are used: very common (≤1/10), common (≤1/100 to <1/10), uncommon (≤1/1,000 to <1/100), rare (≤1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

**General disorders and administration site conditions:**

Very rare: erythema, scales, burning and itching at the application site.

No systemic adverse effects are expected. Reported signs and symptoms at the application site were mild and transient.

**DOSAGE AND ADMINISTRATION**

**Adults**

For topical use on fingernails, toenails and immediately adjacent skin (perionychium, hyponychium).

RejuveNail Anti-fungal nail lacquer is applied in a thin layer once a day on the affected nail/s after washing and drying. The medicated nail lacquer is to be applied over the entire nail plate, 5 mm of surrounding skin and, if possible, under the free edge of the nail. RejuveNail Anti-fungal nail lacquer needs about 30 seconds for drying. The treated nails should not be washed for at least six hours, therefore, application in the evening before going to bed is recommended. After that time, normal hygienic practices can be followed.

RejuveNail Anti-fungal nail lacquer does not need to be removed by any solvent or abrasives (i.e. nail filing), as it is washed off in water. In case of unintentional removal by washing, RejuveNail Anti-fungal nail lacquer can be applied again.

Regular removal of the nail free edge and any onycholitic material by nail clipping is recommended.

It is not recommended to use cosmetic nail polish or other nail cosmetic products on the treated nails.

Treatment should be continued until complete mycological and clinical cure is achieved and healthy nail has grown again. Normally, complete cure of fingernails is achieved in about 6 months while for toenails it takes from 9 to 12 months.

The control of fungal culture should be done 4 weeks after the end of the treatment to avoid interference with culture results by possible residues of active substance.

**Children**

Safety and effectiveness in children below the age of 18 years have not been established, therefore, RejuveNail Anti-fungal Nail Lacquer is not recommended for use in children.

**OVERDOSAGE**

There is no experience of overdose with ciclopirox preparations. However, no relevant systemic effects would be expected to occur if RejuveNail Anti-fungal Nail Lacquer were applied to large areas or used too frequently.
In case of accidental ingestion, contact the Poisons Information Centre on 131126 for advice.

PRESENTATION AND STORAGE CONDITIONS

80mg/g ciclopirox solution in a 6.6mL clear glass bottle, with screw cap fitted with a brush applicator.

Store below 30°C.

Once the bottle has been opened RejuveNail Anti-fungal Nail Lacquer is suitable for use for 6 months if stored as directed.

Special Precautions for Storage

Store the bottle in the outer carton, in order to protect the product from light. The bottle should be kept tightly closed, to avoid evaporation of the content.

Do not refrigerate.

At temperatures below 15°C the medicated nail lacquer may gel. Light flocculation or formation of a light sediment may also occur which can be reversed by warming up to room temperature (25°C) through rubbing the bottle between hands until the solution is clear again (about one minute). This has no impact on product quality or performance.

This product is flammable. Keep away from heat and open flame.

NAME AND ADDRESS OF SPONSOR

A. Menarini Australia Pty Ltd
Level 8, 67 Albert Ave
Chatswood NSW 2067

POISON SCHEDULE

S2 - Pharmacy Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 May 2012

DATE OF MOST RECENT AMENDMENT

1 March 2013