

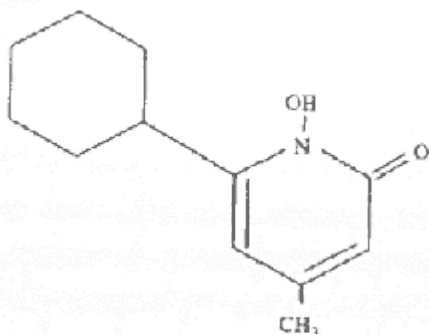
APO-CICLOPIROX

1. APO-CICLOPIROX (8% w/w Nail Lacquer)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciclopirox 8% w/w

Chemical Structure:



Chemical Name: 6-cyclohexyl-1-hydroxy-4-methyl-2-(1H) pyridine.

Empirical Formula: C₁₂H₁₇NO₂

Molecular Weight: 207.3

CAS No.: 29342-05-0

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.

Excipient(s) with known effect

APO-CICLOPIROX is lactose free and gluten free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

APO-CICLOPIROX 8% w/w nail lacquer is a clear, colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APO-CICLOPIROX is indicated for the topical treatment of fungal infections of the nails, caused by dermatophytes, yeasts or moulds, including tinea pedis, tinea cruris and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporium canis*, candidiasis due to *Candida albicans* and tinea (pityriasis) versicolor due to *Malassezia furfur*.

4.2 Dose and method of administration

Dose

Adults

1. Before starting treatment, remove any loose nail or nail pieces using nail clippers or nail files. If you have diabetes or problems with numbness in your toes or fingers, talk to your doctor before trimming your nails or removing any nail pieces.
2. Apply APO-CICLOPIROX every other day for the first month (bedtime is best) to all affected nails with the applicator brush provided. Application may be reduced to not less than twice weekly in the second month of treatment and to once weekly from the third month of treatment. Apply APO-CICLOPIROX evenly over the entire nail and the skin right around the nail. Where possible, APO-CICLOPIROX should also be put on the bottom side of the nail and the skin beneath it. This ensures that the nail is saturated with the active ingredient. Let APO-CICLOPIROX dry (about 30 seconds) before putting on socks or stockings. After putting on APO-CICLOPIROX, wait 8 hours before taking a bath or shower.
3. Apply APO-CICLOPIROX over the previous coat.
4. Once a week (every 7 days), remove APO-CICLOPIROX with a commercial nail polish remover. Remove as much as possible of the damaged nail using scissors, nail clippers, or nail file.
5. Repeat process (steps 2 through 4).

Up to 48 weeks of using APO-CICLOPIROX every other day and having your doctor remove the loose, infected nail as often as monthly is usually how long it takes to get a clear or almost clear nail (which means that 10% or less of your nail is still affected). You may need as long as six months of treatment before you first notice your nail(s) getting better.

Children

Because of the lack of clinical experience, APO-CICLOPIROX is not recommended for use in children.

Method of administration

Topical application

Maximum Tolerated Daily Dose

APO-CICLOPIROX may be used up to one daily

4.3 Contraindications

Hypersensitivity to ciclopirox or any other component in the lacquer listed in section 6.1

4.4 Special warnings and precautions for use

Patients should use the medication for the full treatment time as advised by the physician.

APO-CICLOPIROX must not be applied to the eye. APO-CICLOPIROX is a known eye irritant. Care should be taken to ensure the patient does not inadvertently transfer APO-CICLOPIROX to the eyes by touching them after applying the lacquer to their fingernails.

APO-CICLOPIROX must not be taken orally and is not for vaginal use.

Patients should inform the physician if the area of application shows signs of increased irritation. If a reaction suggesting sensitivity or chemical irritation should occur with the use of APO-CICLOPIROX, treatment should be discontinued and appropriate therapy instituted.

The effectiveness and safety in the following populations have not been studied, as the clinical trials with ciclopirox topical solution 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. These patients should be carefully evaluated as to the suitability of APO-CICLOPIROX for use in treatment of fungal infection.

There is no clinical experience with the efficacy of APO-CICLOPIROX when used with cosmetic nail varnishes.

Paediatric population

Safety and effectiveness in children below the age of 18 years have not been established, therefore, APO-CICLOPIROX is not indicated for use in children.

Elderly population

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.

Avoid the use of occlusive dressings.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetics Interactions

Nil known.

Pharmacodynamic Interactions

Nil known.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3

"Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of increased occurrence of foetal damage, the significance of which is considered uncertain in humans".

Reproduction studies revealed no significant evidence of impaired fertility in rats orally exposed to ciclopirox in dosages of up to 5mg/kg body weight (approximately 5 times the maximum recommended topical human dose based on surface area). No fetotoxicity due to ciclopirox was observed in the mouse, rat, rabbit and monkey at oral dosages of up to 100, 30, 30 and 50mg/kg body weight, respectively (approximately 37.5, 30, 44 and 77 times, respectively, the maximum recommended topical human dose based on surface area). By the dermal route of administration, no fetotoxicity due to ciclopirox was observed in the rat and rabbit at dosages of up to 120 and 100mg/kg body weight, respectively (approximately 121 and 147 times, respectively, the maximum recommended topical human dose based on surface area).

There are no adequate or well controlled studies of topically applied ciclopirox in pregnant women. APO-CICLOPIROX should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

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 APO-CICLOPIROX is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

4.8 Undesirable effects

APO-CICLOPIROX is generally well tolerated. Where APO-CICLOPIROX has come into contact with skin adjacent to the nail, a light reddening or scaling of the skin has been observed in some cases. In isolated cases with APO-CICLOPIROX, transient local reactions e.g. pruritus or a burning sensation may occur, as may - rarely - allergic contact dermatitis.

A 21 day Cumulative Irritancy Study conducted in conditions of semioclusion, a method which applies an appreciably greater stress than normal application of lacquer to the nails and adjacent skin. Mild reactions were seen in the occluded skin in 46% of patients with lacquer, 32% with the base and 2% with the negative control, but all were slight reactions of mild transient erythema. There was no evidence of allergic contact sensitisation for either the lacquer or the vehicle base.

In vehicle controlled clinical trials, 9% (30/327) of patients treated with ciclopirox 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 materials. Four patients (4/327) withdrew due to TEAEs. These were severe tenderness, burning and bleeding of nail beds after treatment with lacquer vehicle; increasing pain beneath nails, irritation of nail beds, increasing periungual erythema and induration after treatment with the lacquer vehicle; increasing paraesthesia in little finger after treatment with lacquer vehicle, and severe rash on the palm of the hand after treatment with ciclopirox lacquer.

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 ciclopirox nail lacquer (5% [16/327]). Other causally related TEAEs included nail disorders such as shape change, irritation, ingrown toenail and discolouration. The incidence of nail disorders was similar between the treatment groups (2% [6/327]) in the ciclopirox 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 treated with ciclopirox nail lacquer (3/327) and vehicle (4/328). In the vehicle controlled studies, one patient treated with ciclopirox nail lacquer discontinued treatment due to a rash that was not causally related to the test material.

The long term safety of ciclopirox nail lacquer has been 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 nail lacquer experienced at least one TEAE that 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.

Post-marketing Experience

Contact dermatitis had been reported during routine post marketing surveillance of ciclopirox.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

There is no experience of overdose with ciclopirox preparations. However, no relevant systemic effects would be expected to occur if APO-CICLOPIROX were applied to large areas or used too frequently.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Other antifungals for topical dermatological use,

ATC code: D01AE14

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. Fe³⁺ and Al³⁺). It thus inhibits the metal-dependent enzymes, including those responsible for the degradation of peroxides within fungal cells.

APO-CICLOPIROX Nail Lacquer should be used for the treatment of fungal infections of the nails. The active ingredient ciclopirox penetrates the nail plate and reaches the fungal pathogen within 48 hours of application.

5.2 Pharmacokinetic properties

Glucuronidation is the main metabolic pathway for ciclopirox,

Absorption

Studies have shown systemic absorption of ciclopirox in patients with dermatophytic onychomycoses, after application of Ciclopirox Nail Lacquer to all 20 digits once daily for six months. Serum and urinary levels were determined approximately every four weeks during treatment and four weeks post-treatment. In this study, ciclopirox peak serum levels ranged from 12-80ng/mL. Total urine levels ranged from 49-4685ng/mL. 23 to 35 days after cessation of treatment, serum and urine levels of ciclopirox were below the limit of detection.

The combined results from two vehicle-controlled studies revealed ciclopirox peak serum levels ranging from 10.0-24.6ng/mL in 24 of 66 (36%) evaluable patients. The lacquer was applied to all toenails and affected fingernails once daily over a period of 48 weeks. It should be noted that 11 patients used concomitant ciclopirox olamine 1% cream.

Other *in vivo* investigations have evaluated the penetration and antifungal activity of the ciclopirox lacquer. In separate studies, healthy volunteers applied ciclopirox nail lacquer to fingernails or toenails daily for up to 45 days. Lacquer was removed once a week. After 7-14 days, there was a high level of biological activity at all depths of the nail increasing to a plateau by 30 days in fingernails and 30-45 days in toenails. These concentrations were substantially higher than those needed for inhibition of growth of dermatophytes that cause onychomycosis.

In vitro investigations have evaluated the penetration and antifungal activity of the ciclopirox lacquer formulation. Radiolabelled ciclopirox applied once to fingernails avulsed (separated from the nail bed) as a result of onychomycosis, demonstrated penetration up to a depth of approximately 0.4mm. Radiolabelled ciclopirox applied to toenails 0.6mm and 1.29mm thick, showed penetration of 0.02-0.04% of the applied dose. After treatment every 3 days for 30 days, the penetration was 0.01-0.07% of the applied dose.

It has been shown that ciclopirox penetrates the nail plate building up a gradient within 14 days of application depending upon the nail condition. Penetration is more rapid and abundant in mycotic nails.

Nails with infection involvement of less than 60% of the of the nail plate, at the start of treatment, have a 4-5 times greater chance of clear regrowth compared to nails showing a higher involvement. 100% clearance rates have been shown in cases of 30% nail plate involvement. When more than 60% of the nail plate is involved, clear regrowth may be reduced to a clinical improvement of approximately 30%.

In another study, three grams of the 1% solution were applied topically to an area of about 750 square centimetres on the back of male subjects for 6 hours. During this time the serum concentration rose to $0.008 \pm 0.005 \mu\text{g/mL}$. Three to 6 hours after removal of the solution, the concentrations had already fallen below the detection limit of $0.003 \mu\text{g/mL}$. Of the radioactivity applied, $1.1 \pm 0.6\%$ was eliminated in the urine and $<0.1\%$ in the faeces; the elimination half-life was $3.5 \pm 1.1 \text{ H}$ on the first day. Excretion was complete on the second and third day. The absorption which can be regarded as equal with the portion of $1.1 \pm 0.6\%$ eliminated in the urine, practically ended when the active substance was removed from the skin.

Microbiology

Ciclopirox is fungistatic and fungicidal against a broad range of fungi and yeast. The Minimum inhibitory concentration (MIC) of ciclopirox for 34 of 35 fungal and yeast strains were between 0.98-3.9 $\mu\text{g/mL}$ (*in vitro*). For *Trichophyton metagrophytes*, the MIC was 7.8 $\mu\text{g/mL}$. 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 31.3 $\mu\text{g/mL}$.

Elimination

Ciclopirox, which is excreted renally in the form of glucuronides within 12 hours of oral administration.

5.3 Preclinical safety data

A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dosed cutaneously twice per week for 50 weeks followed by a 6 month drug free observation period prior to necropsy revealed no evidence of tumours at the application site.

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster cells, with and without metabolic activation (positive); gene mutation assays in the

HGPRT-test with V79 Chinese hamster cells (negative); and a primary DNA damage assays (i.e. unscheduled DNA synthesis assay in A549 human cells) (negative). In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5000mg/kg.

Other

Clinical Trials

The results of use of ciclopirox nail lacquer in treatment of onychomycosis of the toenail without lunular involvement have been obtained from two double-blind, placebo controlled studies. In these studies, patients with onychomycosis of the great toenails without lunular involvement were treated with ciclopirox topical solution 8%, in conjunction with the monthly removal of the unattached, infected toenail. Ciclopirox nail lacquer was applied for 48 weeks. At baseline, patients had 20-65% involvement of the target great toenail plate.

The primary efficacy variable was time to treatment success (negative culture, negative KOH, $\leq 10\%$ affected nail area). For per protocol (PP) at endpoint, 8% (8/103) and 12% (13/111) of subjects in the ciclopirox group, and 1% (1/101 and 1/109) of subjects in the vehicle group had achieved treatment success (Cochran-Mantel-Haenszel [CMH] p-value = 0.018).

The secondary efficacy results are tabulated below.

Secondary Efficacy Variables at Endpoint (PP)						
	Study A			Study B		
	Active	Vehicle	CMH p-value	Active	Vehicle	CMH p-value
Therapeutic Success $\leq 10\%$ involvement and negative culture	10/107 (9%)	1/103 (1%)	0.005	18/114 (16%)	1/111 (1%)	<0.001
Mycological Cure negative culture and negative KOH*	30/102 (29%)	13/100 (13%)	0.001	37/109 (34%)	9/109 (8%)	<0.001
Negative Culture	91/107 (85%)	40/103 39%	<0.001	94/114 (83%)	49/112 (44%)	<0.001

*KOH microscopy does not distinguish living fungi from dead filaments trapped in the nail until they grow out up to a year or more later. Culture results are clinically more relevant.

Two double-blind, placebo-controlled studies have provided data on the use of ciclopirox nail lacquer in the treatment of onychomycosis of the fingernails. A total of 96 patients were treated with ciclopirox nail lacquer and 99 treated with vehicle placebo, for 24 weeks. Negative culture was achieved in a statistically significant number of patients, compared to placebo (81% vs 46% and 62% vs 41%). Great improvement and/or clinical cure was not statistically significant due to the short treatment duration and the inclusion of patients with too great a percentage of nail involvement.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients of APO-CICLOPIROX are:

- Gantrez ES-435
- Ethyl acetate
- isopropyl alcohol

The excipients ethyl acetate and isopropyl alcohol are solvents that vaporise after application.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 2 years from the date of manufacture.

6.4 Special precautions

Store at or below 25°C

Protect from heat light and moisture. (e.g. leave bottle in carton or replace it in carton after use).

Flammable keep away from heat and flame

Instructions for Handling

To prevent the solution from drying upkeep the bottle tightly closed

To prevent the screw cap from sticking to the bottle, avoid spilling solution on the screw thread.

6.5 Nature and contents of container

APO-CICLOPIROX 8%w/w nail lacquer: 9ml Glass Bottles containing 6.6ml of solution.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Glenfield
AUCKLAND 0627

Telephone: (09) 444 2073

Fax: (09) 444 2951

E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

14 January 2010

10. DATE OF REVISION OF THE TEXT

03 February 2017

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new guideline for data sheet.
2	Updated how the information was presented
4.2	Additional information based on new data sheet format.
4.4	Spelling correction, warning section reworded and additional warnings to added
4.8	Additional information based on new data sheet format.
4.9	Additional information based on new data sheet format.
5.1	Additional information based on new data sheet format.
6.1	Updated how the information was presented
6.6	New section and information required in new data sheet format
8	Email contact information added
9	New section and information required in new data sheet format
10.	New date of amendment
Summary Table of Changes	New section and information required in new data sheet format