

Data Sheet

Batrafen Nail Lacquer

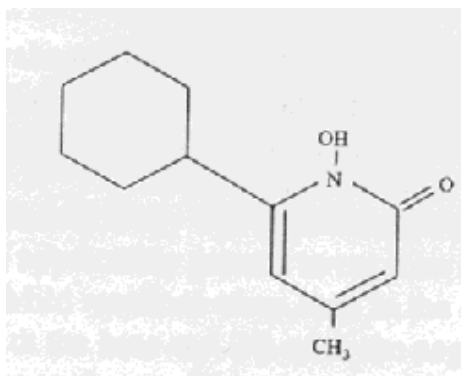
Name of Medicine

Ciclopirox 8% Nail Lacquer

Presentation

Batrafen Nail Lacquer contains 80mg/g (8%) of the active ingredient ciclopirox. Ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2-(1H) pyridone (C₁₂H₁₇NO₂). MW: 207.3.

The chemical structure is shown below:



CAS 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.

The lacquer is composed of butyl ester of PVM/MA copolymer, ethyl acetate and propyl alcohol. The excipients ethyl acetate and propyl alcohol are solvents that vaporise after application.

Batrafen Nail Lacquer is a clear, slightly yellow solution.

Uses

Actions

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.

Batrafen Nail Lacquer has been developed 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.

Pharmacokinetics

Glucuronidation is the main metabolic pathway for ciclopirox, which is excreted renally in the form of glucuronides within 12 hours of oral administration.

Systemic absorption of ciclopirox was determined in patients with dermatophytic onychomycoses, after application of Batrafen 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.

Further *in vivo* investigations evaluated the penetration and antifungal activity of the ciclopirox lacquer formulation. In separate studies, healthy volunteers applied Batrafen Nail Lacquer to the 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 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 good 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.

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%.

Microbiology

Ciclopirox is fungistatic and fungicidal against a broad range of fungi and yeast. The MIC of ciclopirox for 34 of 35 fungal and yeast strains were between 0.98–3.9µg/mL (*in vitro*). For *Trichophyton metagrophytes*, 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.

Clinical Trials

The results of use of Batrafen Nail Lacquer in treatment of onychomycosis of the toenail without lunular involvement were 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 by the investigator. Batrafen 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, ≤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 312			Study 313		
	Active	Vehicle	CMH p-value	Active	Vehicle	CMH p-value
Therapeutic Success ≤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 provided data on the use of Batrafen Nail Lacquer in the treatment of onychomycosis of the fingernails. A total of 96 patients were treated with Batrafen 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.

Indications

Fungal infections of the nails, caused by dermatophytes, yeasts or moulds.

Dosage and Administration

Adults

Before applying Batrafen Nail Lacquer for the first time, as much as possible of the affected nail material should be removed e.g. with scissors, and the remaining diseased nail roughened with a nail file.

Unless otherwise directed, Batrafen Nail Lacquer is applied to the diseased nail in a thin layer every other day for the first month. This ensures that the nail is saturated with the active ingredient. 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 onwards.

Throughout the application period, the entire coating of lacquer is taken off once a week with a commercial nail varnish remover. During this period, as much as possible of the affected nail material should again be removed, using a nail file. If the coating of lacquer is damaged in the meantime, it is sufficient to paint over the chipped areas again with Batrafen Nail Lacquer.

The duration of application depends upon the severity of the infection. A period of six months' treatment should not be exceeded because of a lack of clinical experience with Batrafen Nail Lacquer beyond this period of time.

One bottle contains approximately 500 applications.

Children

Because of the lack of clinical experience, Batrafen Nail Lacquer is not recommended for use in children.

Contraindications

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

Batrafen Nail Lacquer should not be used in pregnancy or lactation.

Warnings and Precautions

Batrafen Nail Lacquer is not for ophthalmic, oral or intravaginal use. Batrafen Nail Lacquer is known to be an eye irritant. Care should be taken to ensure the patient does not inadvertently transfer Batrafen 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 Batrafen Nail Lacquer, treatment should be discontinued and appropriate therapy instituted.

So far there is no relevant clinical experience with patients who have 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), who are immunocompromised (e.g. HIV-infected patients, transplant patients), or have a diabetic neuropathy. These patients should be carefully evaluated as to the suitability of Batrafen Nail Lacquer for use in treatment of fungal infection.

There is no clinical experience with the efficacy of Batrafen Nail Lacquer when used with cosmetic nail varnishes.

Carcinogenesis, mutagenesis, impairment of fertility

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.

Use in pregnancy

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. Batrafen 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 Batrafen Nail Lacquer is administered to a nursing woman.

Use in children

Safety and effectiveness in children below the age of 18 years have not been established, therefore, Batrafen Nail Lacquer is not indicated for use in children.

Use in elderly patients

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.

Adverse Effects

Batrafen Nail Lacquer is generally well tolerated. Where Batrafen 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.

A 21 day Cumulative Irritancy Study was 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 Batrafen 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 Batrafen 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 Batrafen 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 Batrafen Nail Lacquer (3/327) and vehicle (4/328). In the vehicle controlled studies, one patient treated with Batrafen Nail Lacquer discontinued treatment due to a rash that was not causally related to the test material.

The long term safety of Batrafen Nail Lacquer 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 Batrafen 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.

Contact dermatitis has been observed during routine post marketing surveillance.

Interactions

Nil known.

Overdosage

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

Pharmaceutical Precautions

Shelf Life

Store at room temperature (below 25°C).

Once the bottle has been opened Batrafen Nail Lacquer is stable for at least 6 months if stored as directed.

Special Precautions for Storage

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

To prevent the solution from drying up, the cap must be firmly screwed down after use.
To prevent the screw cap from sticking to the bottle, avoid spilling solution on the screw thread.

Medicine Classification

Pharmacist Only Medicine.

Package Quantities

3g glass bottle, with screw cap, which are fitted with a brush.

Further Information

Nil

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Date of Preparation

13 August 2007