SUPPORTED BY AN EDUCATIONAL GRANT FROM
DERMIK LABORATORIES

Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis

Aditya K. Gupta, MD, FRCP(C),[a] Philip Fleckman, MD,[b] and Robert Baran, MD[c]
Toronto, Ontario, Canada, Seattle, Washington, and Cannes, France

Background: Onychomycosis is a relatively common condition affecting toenails more than fingernails. It is caused predominantly by dermatophytes. Onychomycosis can cause pain and discomfort and has the potential to be a source of morbidity.

Objective: We evaluated the efficacy and safety of ciclopirox nail lacquer solution 8% used to treat onychomycosis of the toe in the United States and in centers worldwide.

Methods: Two identically designed, double-blind, vehicle controlled, parallel group multicenter studies were performed in the United States to evaluate the use of ciclopirox nail lacquer to treat mild to moderate toe onychomycosis caused by dermatophytes. In the first study, 223 patients were randomized to treatment (ciclopirox group: 112, vehicle group: 111), and in the second study, 237 subjects were randomized (ciclopirox group: 119, vehicle group: 118). Before randomization, patients were to have clinical features of onychomycosis in at least one great toe with positive light microscopic examination and a positive dermatophyte culture. The test material was applied daily for a period of 48 weeks to all toenails and affected fingernails, covering the entire nail plate and approximately 5 mm of surrounding skin. At baseline, subjects had between 20% to 65% area of target nail involved. Physician's assessments were carried out every 4 weeks, and mycologic evaluation and photographic planimetry using standardized photographs were performed every 12 weeks during the 48 weeks of treatment. In studies conducted outside the United States, patients were also to have clinical, microscopic, and culture evidence of onychomycosis. However, these studies included some patients infected with nondermatophyte organisms (eg, *Candida* species), and the area of nail involvement was generally greater than observed in the US studies. Treatment regimens also varied in the non-US studies with lacquer applications that were sometimes less frequent than the once daily treatment used in the US studies (eg, alternate day or twice weekly). In addition, the typical duration of treatment was 6 months in the non-US studies as compared with 48 weeks in the United States. Outcome measures were similar to those used in the US trials, although a non-photographic planimetric method was used to quantify disease extent.

Results: Data from the pivotal US trials have demonstrated that ciclopirox nail lacquer 8% topical solution is significantly more effective than placebo in the treatment of onychomycosis caused by *Trichophyton rubrum*, and of mild to moderate toe onychomycosis without lunula involvement. At the end of the 48-week treatment period, the mycologic cure rate (negative culture and negative light microscopy) in study I was 29% vs 11% in the ciclopirox and vehicle groups, respectively. Similarly, the mycologic cure rate for study II was 36% vs 9%, respectively. In the non-US studies, the mycologic cure rates ranged from 46.7% to 85.7%. In addition, ciclopirox nail lacquer has demonstrated a broad spectrum of activity with efficacy against *Candida* species and some nondermatophytes in non-US studies. Ciclopirox nail lacquer is considered extremely safe regarding causally related treatment emergent adverse-effects (TEAEs), with most TEAEs transient and localized to the site of action (eg, erythema and application site reaction). In the US studies, TEAEs were generally mild and cleared while the patient continued to use the nail lacquer.

Conclusions: Studies conducted worldwide demonstrate the efficacy of ciclopirox nail lacquer for the treatment of finger and toe onychomycosis. Both controlled and open-label studies confirm the excellent

From the Division of Dermatology, Department of Medicine, Sunnybrook and Women's College Health Sciences Center (Sunnybrook site), and the University of Toronto,[a] the Division of Dermatology, Department of Medicine, University of Washington, Seattle,[b] and the Nail Research Center, Cannes.[c]
This article is part of a supplement sponsored by Aventis.
Dr Baran and Dr Fleckman have been consultants for Aventis. Dr Gupta has been a consultant for Aventis, Janssen, Novartis, and Pfizer.
Reprint requests: Aditya K. Gupta, MD, FRCP(C), 490 Wonderland Road South, Ste 6, London, Ontario Canada N6K 1L6.

0190-9622/2000/$12.00 + 0 **16/0/109071**
doi:10.1067/mjd.2000.109071

safety profile of this topical therapy. Thus, the nail lacquer provides a treatment choice with a favorable benefit-to-risk ratio. With its novel mechanism of action and its topical route of administration, ciclopirox nail lacquer offers an innovative approach to the treatment of this often difficult-to-manage disease. (J Am Acad Dermatol 2000;43:S70-80.)

Ciclopirox and its salt ciclopirox olamine are hydroxypyridone derivatives that differ chemically and mechanistically from other marketed antifungal agents such as the azoles and the allylamines.[1-5] Unlike most antifungals currently available, ciclopirox does not affect sterol biosynthesis. Ciclopirox is glucuronidated and is not metabolized via the cytochrome P_{450} pathway. The novel antifungal action of ciclopirox involves chelation of polyvalent cations (such as Fe^{3+}) with inhibition of metal-dependent enzymes responsible for the degradation of toxic peroxides in the fungal cell.[6]

Ciclopirox is a broad spectrum antifungal agent that is effective against the major human fungal pathogens responsible for onychomycosis.[7-11] In fact, ciclopirox is fungicidal in vitro to strains of *Trichophyton rubrum, T mentagrophytes,* and *Epidermophyton floccosum,* the fungal species typically implicated as the causative organisms in onychomycosis.[7] In vitro, ciclopirox is also effective against *Candida* sp and nondermatophyte molds, for example, *Scopulariopsis brevicaulis, Aspergillus* sp, and *Scytalidium hyalinum.*[9,10]

Ciclopirox olamine was first introduced to the market in April 1975, and is now marketed in more than 70 countries worldwide. Ciclopirox olamine has been marketed as a 1% cream and lotion in the United States for 15 years and worldwide for 24 years. It was recently approved as the 0.77% gel in the United States. Ciclopirox nail lacquer topical solution 8% (also referred to in this article as ciclopirox nail lacquer) was first approved for use in France in 1991. Since then, the product has been approved for use in over 40 countries and has most recently been approved in the United States in December 1999 for the topical treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement in immunocompetent individuals infected by *T rubrum.*

Onychomycosis is a common condition; some estimates suggest that it affects approximately 6% to 13% of the North American population.[12,13] Onychomycosis is present predominantly in toenails rather than fingernails, in males, and in the elderly, and is most commonly caused by *T rubrum*. Invasive nail disease caused by molds is less common in North American series. *Candida* sp are more likely to cause invasive nail disease in fingernails than toenails in immunocompetent individuals. Onychomycosis may have medical significance especially in some disease states such as diabetes and others where the individual is immunocompromised.[14] Also, onychomycosis can have a substantial effect on the activities of daily living, such as ambulation.[15]

In the United States, griseofulvin and ketoconazole were the only available treatments approved for onychomycosis until oral itraconazole became available for this indication in October 1995.[16,17] Subsequently, oral terbinafine was approved for the treatment of tinea unguium in May 1996. Oral fluconazole is not approved in the United States for this indication. Ciclopirox nail lacquer is the first non-oral agent approved in the United States for the management of onychomycosis. This article focuses on the 2 pivotal studies conducted in the United States that confirmed the efficacy and safety of ciclopirox nail lacquer for the treatment of mild to moderate toenail onychomycosis. In addition, results from non-US studies are also summarized.

Two identically designed, double-blind, vehicle-controlled, parallel group, multicenter studies were performed to evaluate the use of ciclopirox nail lacquer in individuals with a diagnosis of mild to moderate distal subungual tinea unguium of at least one great toenail. These two pivotal trials were conducted in the United States to meet the regulatory requirements necessary for confirming the efficacy and safety of an investigational drug.

MATERIALS AND METHODS FOR THE UNITED STATES STUDIES

Study design

Baseline evaluation included recording information such as demographic data, medical history, duration of onychomycosis, and the presence or absence of chronic tinea pedis. A physical examination was conducted; clinical laboratory and mycologic sampling was carried out, ensuring that the eligibility criteria were met. Each eligible subject was randomly assigned to receive either the active treatment or matching vehicle for 48 weeks. Subjects reported to the clinic for evaluations by the physician every 4 weeks. If a subject had a clinically and mycologically cured target nail (treatment cure) at the conclusion of the 48 week treatment period, the

patient was eligible for post-treatment follow-up evaluations for a 12 to 24 week period.

Inclusion criteria included individuals age 18 to 70 years with distal subungual tinea unguium of at least one great toenail (target nail). Before randomization, patients were to have clinical evidence of onychomycosis with positive potassium hydroxide (KOH) preparation and positive dermatophyte culture. Subjects had between 20% to 65% area of target nail involved (confirmed by computerized planimetry of standardized photographs). Subjects were excluded if either white superficial or proximal subungual onychomycosis was present. Also excluded were subjects with abnormalities of the target nail that could have prevented obtaining a normal appearing nail if complete cure of the tinea unguium was achieved. Similarly, individuals with a structural deformity of the target nail or foot that could interfere with photography or planimetric analysis were excluded. An individual with a "spike" of onychomycosis extending to the cuticle of the target nail could not enter the study. A patient with a history of immunosuppression or clinical signs indicative of possible immunosuppression was not allowed to enroll in the study.

Subjects were not allowed to use systemic antifungal therapy within 24 weeks before the screening visit; however, local treatment of vaginal candidiasis and the use of ciclopirox olamine cream 1% for treating flares of tinea pedis were allowed. Patients could not use topical antifungal therapy within 14 days of the screening visit; however, no washout period was required for ciclopirox olamine cream 1%.

Treatment procedures

The test material was applied daily, approximately 24 hours apart, with the lacquer brushed on all toenails and any affected fingernails. Subjects were instructed to apply the material to all toenails regardless of involvement. The areas covered with the lacquer were the entire nail plate and approximately 5 mm of adjacent skin. If possible, the material was applied to the nail bed, the hyponychium, and the ventral surface of the nail plate where it was free of the nail bed. Patients were to wait at least 8 hours after application of the lacquer before washing the feet.

The nail lacquer was not removed on a daily basis; rather daily applications were applied over the previous coat. Every 7 days subjects were instructed to completely remove the lacquer with isopropyl alcohol swabs, file away any loose nail material, and trim the nails as necessary.

Normal hygiene and foot care practices were permitted. No occlusive dressings were allowed. At each visit the target nail was trimmed to at least the distal groove or an onycholytic nail was trimmed to the point of attachment. Any excess horny material was filed from the nail surface before treatment application. Excessive debridement or drilling of nails was not permitted. As per protocol, fungal infections besides onychomycosis (eg, tinea pedis or tinea cruris) were treated with ciclopirox olamine cream 1%. Subjects were not allowed to apply any product other than the nail lacquer on the treated nails.

Method of assessment

The efficacy variables pertained to the target nail and included the KOH examination and fungal culture of material obtained from the nail, planimetric measurement of the involved area, and a physician's global evaluation. The global evaluations were performed at each 4 week clinic visit, whereas the mycologic evaluations and photographic planimetry measurements were performed every 12 weeks during the 48 week treatment.

Planimetry

Computerized planimetric measurements of the involved area of the target nail were made from standardized photographs and analyzed at a central laboratory in a blinded fashion. Using a fine point felt tip pen, the investigator outlined the portion of target nail that was clinically involved and the boundary of the hyponychium or nail groove. The photographs were scanned into a computer and a planimetric measurement of the area of target nail involved was performed. The affected area (which included visually involved nail plus any area of missing nail because of trimming back from the distal groove) as a percentage of the whole nail area was used for the analysis. Computerized photoplanimetry is reproducible; however, because areas are delineated by ink lines with a finite thickness, and because the final length of the healthy nail can only be presumptive, loss of precision is inevitable as a treatment cure is approached. Thus, planimetry cannot be used to distinguish minimal residual disease from cure. Hence, the establishment of cure remained a clinical decision.

Global evaluation score

The global evaluation score (GES) of the target nail was assessed visually by comparing subsequent evaluations to the Day 1 (baseline) evaluation. The 5-point grading scale was, 0 = cleared (100% clearance of clinical signs of disease corroborated by an absence of investigator markings on the photograph), 1 = excellent improvement (≥ 75% but <100% clearance of clinical signs of disease), 2 =

Table I. Demographic and background characteristics (intention to treat, ITT population)

	Study I (Study 312)		Study II (Study 313)	
	Ciclopirox	Vehicle	Ciclopirox	Vehicle
Total number of subjects treated (ITT population)	112	111	119	118
Sex				
Male	85 (76%)	90 (81%)	94 (79%)	89 (75%)
Female	27 (24%)	21 (19%)	25 (21%)	29 (25%)
Age (years)				
Mean (±SD)	50.4 (±12.3)	48.6 (±13.2)	49.6 (±11.9)	50.1 (±12.2)
Range	20-70	18-70	19-70	23-70
Area of target nail involved (%)				
Mean (±SD)	39.6 (±10.0)	40.3 (±9.6)	37.7 (±10.8)	38.3 (±8.6)
Range	20-63	20-63	20-65	21-62
Duration of onychomycosis at the target nail (years)				
Mean	11.8	11.1	10.8	11.6
Range	0.6-44	0.3-50	0.5-51	0.5-50
Causative organism (n [%])				
T rubrum	108 (96%)	108 (97%)	114 (96%)	112 (95%)
T mentagrophytes	4 (4%)	3 (3%)	5 (4%)	5 (5%)
E floccosum	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)

moderate improvement (≥ 50% to <75% clearance of clinical signs of disease), 3 = slight improvement (<50% clearance of clinical signs of disease), 4 = no change (no detectable improvement from baseline evaluation), and 5 = exacerbation (flare of area being studied or increase in area of involvement).

Efficacy criteria

The efficacy criteria pertained to the target toenail and were based on the following: fungal culture, light microscopic examination (KOH exam), physician's GES, and affected area as a percentage of the whole nail plate area (planimetry). The primary efficacy variable was treatment success (defined as simultaneous negative KOH and culture, and ≤ 10% area involvement of the target nail plate as determined by planimetry). Other secondary variables included: treatment cure (defined as simultaneous negative KOH and culture, and a GES of cleared), mycologic cure (defined as simultaneous negative KOH and culture), and negative mycologic culture.

Safety criteria

Adverse events (AEs) were recorded during the study, and were defined as any signs, symptoms, illnesses, or diagnoses that appeared or worsened. For example, flares of tinea pedis, skin irritation adjacent to the treated nails, or nail bed irritation were reported as AEs. All AEs that occurred at any time during the study, whether believed by the investigator to be related or unrelated to the test material, were reported as an AE. For the safety analysis, only treatment-emergent AEs (TEAEs) were considered. This included any AE occurring during treatment that was not present before treatment or was present before treatment but became more intense (that is, increased in severity or frequency) during the treatment period. In addition to continuous AE monitoring, clinical laboratory evaluations (complete blood count, serum chemistry including liver function tests and electrolytes, and urinalysis) were performed every 12 weeks during the 48 week study. At selected study sites blood samples were collected before, during, and after treatment for measurement of serum levels of ciclopirox and its glucuronide metabolite.

Statistical analysis

Descriptive statistics were used to summarize the patients' demographic characteristics (age, gender, race) and the background characteristics (percent area of involvement of the target great toenail, duration of onychomycosis, causative organism, presence/absence of tinea pedis). Area of involvement at baseline (less than or greater than 40% of nail surface) was also used as a stratification variable in the efficacy analyses. The age of the subject, percentage involvement of nail plate at the baseline visit, and the duration of onychomycosis were considered as continuous variables and compared by means of the analysis of variance (ANOVA) between the 2 treatments without any adjustments. The other variables

Table II. Efficacy results for week 48 (last observation carried forward*; ITT population)

	Study I			Study II		
Efficacy parameter	Ciclopirox	Vehicle	CMH *P* value†	Ciclopirox	Vehicle	CMH *P* value†
Mycologic cure‡	30/105 (29%)	12/106 (11%)	.002§	41/115 (36%)	10/114 (9%)	<.001§
Treatment success‖	7/107 (6.5%)	1/108 (0.9%)	.031§	14/116 (12%)	1/115 (0.9%)	.001§
Treatment cure¶	6/110 (5.5%)	1/109 (0.9%)	.059	10/118 (8.5%)	0/117 (0%)	.001§
Negative culture	94/112 (84%)	41/111 (37%)	<.001§	100/119 (84%)	52/118 (44%)	<.001§

*Last available follow-up measurement for each subject.
†*P* value for treatment difference from Cochran-Mantel-Haenszel test adjusting for center.
‡Mycologic cure: negative KOH and negative culture.
§Statistically significant.
‖Treatment success: ≤10% target nail plate involvement and negative KOH and negative culture.
¶Treatment cure: negative culture and negative KOH, global evaluation score = cleared.

Table III. Treatment emergent adverse events (TEAEs) reported by more than 1 patient and considered by the investigator to be possibly related to test material

	Study I		Study II	
	Ciclopirox	Vehicle	Ciclopirox	Vehicle
Total number of subjects treated	112	111	119	118
Number with related TEAEs	10 (9%)	7 (6%)	16 (13%)	9 (8%)
Application site reaction*	3 (3%)	2 (2%)	0	1 (1%)
Nail disorder†	2 (2%)	1 (1%)	3 (3%)	4 (3%)
Rash‡	4 (4%)	1 (1%)	12 (10%)	2 (2%)

*eg, tingling sensation, pain, or intermittent burning.
†eg, changes in nail shape or color.
‡eg, localized erythema.

were considered as categorical and the Cochran-Mantel-Haenszel test adjusted for the investigator site was used. All subjects who had received at least one dose of the randomized study medication were included in the intent-to-treat (ITT) population. The primary time point of interest was end of treatment (typically week 48), although interim time points were also analyzed. This conservative approach (known as a Last Observation Carried Forward method of analysis) assumed that a subject would not have achieved treatment success or treatment cure if he or she remained in the study.

RESULTS OF US STUDIES

Study patients

In the first study (Study 312), a total of 223 individuals were randomized to treatment and were included in the ITT analysis (ciclopirox group: 112, vehicle group: 111). Of the patients randomized to treatment, 89 (79.5%) and 84 (75.7%) completed the study for the active and vehicle group, respectively. Similarly, 237 subjects were randomized to treatment in study II (Study 313) and were included in the ITT analysis (ciclopirox: 119 subjects, vehicle: 118). Of the patients randomized to treatment in this study, 96 (80.7%) and 94 (79.7%) completed the study, respectively. None of the 231 patients receiving the ciclopirox treatment in either study discontinued the study prematurely because of an AE. The primary reasons for being withdrawn from the study for both the ciclopirox and vehicle groups included: withdrawal of consent, unreliability, violation of protocol criteria, lost to follow-up, and lack of efficacy.

Demographic and baseline characteristics for study I and study II are presented in Table I. Population characteristics were homogenous between the two treatment groups ($P > .05$) and consistent across studies. The studied population was predominantly male (approximately 80%), with a mean age of approximately 49 years. In addition, the mean area of involvement for the target toenail was approximately 40%, and the predominant causative pathogen was *T rubrum*.

The most frequently used non-study medication was ciclopirox olamine cream 1%, for the treatment of any tinea pedis flares that may have occurred dur-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.