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Ciclopirox Nail Lacquer Topical Solution 8%

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ABSTRACT

*Ciclopirox nail lacquer 8% (Penlac, Aventis Pharma) was approved by the US FDA in December 1999, as a component of a comprehensive management program, for use in immunocompetent patients who have mild to moderate onychomycosis of the fingers and toes without lunula involvement due to *Trichophyton rubrum*. The comprehensive management program includes removal of the unattached, infected nails as frequently as once per month, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures. The nail lacquer is not approved in Canada.*

KEY WORDS: *onychomycosis, management*

In North America there are no other approved topical therapies for the treatment of onychomycosis. However, amorolfine is used in Europe and results¹ are comparable to those found with ciclopirox nail lacquer. Oral treatments approved in North America for the management of onychomycosis are terbinafine and itraconazole. In some countries fluconazole is also approved.

Mechanism of Action

The exact mechanism of action is not known. However, investigators have shown that ciclopirox has a high affinity for polyvalent cations such as Fe³⁺ and Al³⁺ and may chelate them.^{2,3} Trapping these essential enzymatic cofactors may have an inhibitory effect on enzymes such as cytochromes, which are involved in the mitochondrial electron transport processes in the course of energy production. As well, ciclopirox may inhibit the activity of catalase and peroxidase, which are responsible for the intracellular degradation of toxic peroxides.³ Other studies have shown that ciclopirox may also impair fungal metabolism by affecting transport mechanisms located in the fungus membrane. In some cells there may be an intracellular depletion of essential amino acids and nucleotides which may result in reduced synthesis of proteins and nucleic acids.³

Pharmacokinetics

When ciclopirox olamine is administered orally it is rapidly absorbed with the majority of the compound undergoing glucuronidation and subsequent renal excretion. In 5 patients with fingernail onychomycosis ciclopirox nail lacquer was applied once daily to all 20 digits and the adjacent 5mm of skin once daily for 6 months.² The mean absorption of ciclopirox was less than 5% of the applied dose with the ciclopirox serum levels ranging from 12-80ng/ml. One month after stopping treatment, the levels of ciclopirox in the serum and urine were below the limit of detection. In another trial patients applied ciclopirox nail lacquer topical solution 8% once daily to all toenails and affected fingernails for 48 weeks.² Twenty-four of 66 randomly chosen patients had detectable ciclopirox levels at some point during the dosing interval ranging from 10.0-24.6ng/ml, usually in the last week of the study. Eleven of the 24 patients with detectable ciclopirox levels were applying ciclopirox olamine cream 0.77% as a concomitant medication, usually for tinea pedis.

This nail lacquer delivery system contains 8% ciclopirox free acid. Following application of the lacquer to the nail plate, the solvents evaporate and the concentration of ciclopirox in the film increases to 34.8%, thus resulting in a high concentration

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gradient, which favors the delivery of the ciclopirox to the dorsal aspect of the nail plate and the nail bed.^{4,5} In excised human toenails, 24 hours following application, labeled ciclopirox nail lacquer was detectable to a depth of 0.4mm.² The nails had a treatment surface of at least 1cm². In general, penetration was observed to be more pronounced if the nail appeared rougher or more fissured.

In a study conducted in 5 healthy volunteers ciclopirox nail lacquer 8% was applied daily to the toenails, and the lacquer was removed once per week. The distal portion of the nail was sampled 7, 14, 30, and 45 days after the start of treatment, and 7 and 14 days post-treatment. After 7 days of application, ciclopirox appeared to be uniformly distributed in all layers of the nail with a concentration of 284-384µg of nail. At day 45 the

concentration of drug in the nail ranged from 1448-1899µg/g of nail. The above concentrations indicate a high level of biological activity at all depths of nail. Fourteen days after treatment was stopped, residual amounts of ciclopirox were detected in the nail, indicating that the levels had decreased substantially.

Clinical trials

Table 1 outlines the results of US clinical studies for ciclopirox. During the 48 week treatment period physicians' assessments were carried out every 4 weeks, and mycological evaluation and photographic planimetry using standardized photographs were performed every 12 weeks. Non-US studies had similar outcome measures, although a non-photographic planimetric method was used to quantify disease extent.

Trial	Disease	n	Treatment Regime	Mycologic Cure Rate*		"Almost Clear" Rate**		Complete Cure Rate***	
				Treatment Group	Vehicle Group	Treatment Group	Vehicle Group	Treatment Group	Vehicle Group
US – I Double-blind Placebo	Dermatophyte Onychomycosis	Ciclopirox grp: 112 Vehicle grp: 111 n=223	Daily for 48 wks to all toenails & affected fingernails, covering entire nail plate + 5mm surrounding skin	29% (30/105)	11% (12/106)	6.5% (7/107)	0.9% (1/108)	5.5% (6/110)	0.9% (1/109)
US – II Double-blind Placebo	Dermatophyte Onychomycosis	Ciclopirox grp: 119 Vehicle grp: 118 n=237	Daily for 48 wks to all toenails & affected fingernails, covering entire nail plate + 5mm surrounding skin	36% (41/115)	9% (10/114)	12% (14/116)	0.9% (1/115)	8.5% (10/118)	0% (0/117)

Table 1: Clinical trial results from US studies.^{2,6}

*Negative culture and negative light microscopic examination

**10% nail involvement and negative mycology

***Clear nail and negative mycology

In studies conducted outside of the US, patients also had clinical, microscopic and culture evidence of onychomycosis. However, these studies included some patients with non-dermatophyte organisms (e.g., *Candida* spp.), and the area of nail involvement was generally greater than that 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 utilized in the US studies (e.g., alternate day or twice weekly). In addition, the typical duration of treatment was 26 weeks in the non-US studies as compared to 48 weeks in the US. Outcome measures were similar to those used in the US trials, although a non-photographic planimetric method was used to quantify disease extent.⁶

The meta-analytic average of mycologic cure rates for US and non-US studies that are randomized, or open studies with ≥50 patients is 52.6 ± 4.2%, (n=2027 patients from 10 studies).⁷ In terms of the clinical response rates, the meta-analytic average for US and non-US studies that are randomized or open studies with ≥50 patients is 53.7 ± 7.4%, (n=2179 patients from 11 studies).⁷

Ciclopirox nail lacquer has demonstrated a broad spectrum of activity with efficacy against *Candida* species and some non-dermatophyte moulds in the non-US studies.^{6,8}

There are limited data to suggest that ciclopirox nail lacquer may have a role in special nail presentations such as a dermatophytoma, lateral onychomycosis, extensive onycholysis, longitudinal streak and a thickened nail, especially when combined with the judicious use of debridement or mechanical/chemical avulsion.^{4,9} Ciclopirox nail lacquer may also prove useful in cases of early recurrence of disease.⁹ It is possible that there may be a role for combination therapy using ciclopirox nail lacquer and oral antifungal agents.^{9,10}

Adverse-effects

Ciclopirox nail lacquer appears to be safe as observed in studies conducted in the US and worldwide. Adverse effects are generally localized and consist primarily of erythema and, less frequently, of a burning/tingling sensation or edema at the application site. Nail disorders such as change in shape, irritation, ingrown nail or discoloration, are also seen.² In most instances the adverse effects

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Treatment Options For The Cutaneous Manifestations Of Systemic Sclerosis

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ABSTRACT

Systemic sclerosis is a multisystem disorder with vascular instability as a clinical hallmark. Treatment currently consists of recognition and management of end-organ damage. Dermatologists can assist in the management of these patients by facilitating early diagnosis, and treating cutaneous manifestations such as Raynaud's phenomenon, cutaneous calcinosis, and digital ulceration. New potentially disease-modifying therapies are now undergoing clinical trials.

KEY WORDS: *systemic sclerosis, scleroderma*

Systemic sclerosis (SSc) differs from localized scleroderma in prognosis as well as clinical expression. Patients have acral sclerosis associated with vascular instability in addition to internal organ involvement. They are seen by both rheumatologists and dermatologists, who participate in the management of cutaneous complications of the disease. The extent of skin involvement is quantified by a skin scoring method that correlates involvement with prognosis and is an accurate reflection of skin biopsy thickness.¹ Systemic sclerosis is commonly divided into the limited form (formerly termed CREST) or the diffuse form. Each of these is associated with clinically "silent" complications about which the clinician should be aware. In limited SSc, a significant proportion of patients develop life-threatening pulmonary hypertension. Baseline electrocardiography, echocardiography and pulmonary function testing may identify individuals at risk.^{2,3} In generalized SSc, renal hypertensive crisis is the silent threat, and periodic blood pressure monitoring is advised. No therapies have been shown in blinded placebo-controlled trials to improve the overall course of systemic sclerosis.⁴ As a result, the current therapy for SSc is to treat the disease's complications. The purpose of this article is to review the management of the cutaneous manifestations of this disease.

Clinical Issues Of Relevance To Dermatologists

Sclerodermatous skin is characterized by increased thickness, dryness, hair loss, pigment alteration, telangiectasis and pruritis. In addition, patients with scleroderma may have an increased risk of cancer. A population-based retrospective cohort study identified a standardized incidence ratio of 4.2:1 for nonmelanoma skin cancer.⁵ Treatment of involved skin includes frequent use of emollients and physical protection from temperature extremes and abrasion. The use of antihistamines and the tricyclic antidepressant, doxepin, can alleviate pruritis.

Raynaud's phenomenon is a triphasic color reaction where the digits turn blue and white in response to cold, followed by a reactive plethora. This is often the presenting sign of SSc and can lead to pain, ulceration and digit loss. Dihydropyridines are the calcium antagonists most often used to treat this because they

have some selectivity for smooth muscle.⁶ Nifedipine in a standard formulation (10 mg Po TID),^{7,8} or in a sustained release ("retard") preparation (10-20 mg PO BID), as well as amlodipine, a long acting dihydropyridine⁹ (10 mg PO OD) have been shown to be effective at reducing pain and vasospasm in double blind placebo-controlled trials. Side effects, including headaches, dizziness, ankle swelling, and flushing can be limiting. Nitroglycerin ointment 1% applied TID to digits can be used as an adjunct and has shown efficacy in terms of reduced frequency of attacks and ulceration.¹⁰ Sustained release patches can also lessen the number and severity of attacks.¹⁰ Again, headaches can be a limiting side-effect. In severe Raynaud's, intravenous iloprost infusion can be used for short-term palliation.¹¹ Oral analogues have, unfortunately, not yet fulfilled their promise.¹² When digital ulceration occurs, low dose acetylsalicylic acid (325 mg OD) can be added.³ Antibiotics and colloid dressings can also be of benefit. Surgical approaches include sympathectomy and limited microsurgical arteriolytic.¹³ Proximal vessel disease should be considered in the presence of digital gangrene, as ulnar artery narrowing has been recognized increasingly in patients with SSc.¹⁴

Cutaneous calcinosis can be the source of both pain and disability in patients with localised SSc. There is no pharmacological treatment that can prevent or reduce calcinosis. Coumadin,¹⁵ colchicine,¹⁶ bisphosphonates,^{17,18} and diltiazem have been tried with variable success.¹⁹ Surgical extirpation can be of benefit for larger lesions²⁰ and smaller lesions can be effectively treated with CO₂ laser.²¹ Impaired healing is variable, as CO₂ laser treatment has been shown to be beneficial for peri-oral rhytids in limited progressive systemic sclerosis.²²

Systemic corticosteroids have been used by dermatologists in the early edematous phase of SSc. A case-controlled study of the use of systemic corticosteroids in SSc suggested an adverse outcome with an odds ratio of 4.37:1 for scleroderma renal crisis.²³ Systemic corticosteroid therapy is, thus, best avoided in patients with SSc. The substitution of other immunosuppressives is suggested for life threatening disease such as myositis, pericarditis or alveolitis.

SSc Cutaneous Manifestations	Possible Treatment/Dose	Side Effects
Raynaud's phenomenon	<ul style="list-style-type: none"> • Nifedipine – standard formulation (10mg po tid) • Nifedipine – re.tard formulation (10-20mg po bid) • Amlodipine (10mg po qd) 	<ul style="list-style-type: none"> • Headaches • Dizziness • Ankle swelling • Flushing
Cutaneous calcinosis	Tried with variable success: <ul style="list-style-type: none"> • Coumadin • Colchicine • Bisphosphonates • Diltiazem • Surgical extirpation • CO₂ laser 	
Digital ulceration	<ul style="list-style-type: none"> • Nitroglycerin ointment 1% applied to digits • Acetylsalicylic acid (325mg qd) • Sympathectomy • Limited microsurgical arteriolyis 	<ul style="list-style-type: none"> • Headaches

Table 1: Cutaneous manifestations in systemic sclerosis and possible treatment options.

Possible Treatment Regimens

No therapy has been shown in controlled clinical trials to be truly disease-modifying. The use of D-penicillamine has been supported by both retrospective²⁴ and prospective²⁵ studies. However, a recent double-blind controlled trial showed no difference in outcome between low dose D-penicillamine (125mg on an alternate day basis) and high-dose D-penicillamine (750-1000mg/day), putting the efficacy of this drug in doubt.²⁶ In a much publicized report on the use of minocycline, only 4 out of 11 patients improved significantly.²⁷ Methotrexate showed promise in a small 24-week randomized double blind trial.²⁸ A larger trial of 70 patients has suggested a trend toward improvement of skin disease, but has not yet been reported in full.²⁹ The recent formulation of guidelines for clinical trials in this disease should allow the determination of the clinical efficacy of these and various new treatment modalities. Recombinant human relaxin is being evaluated and may result in clinically significant skin score improvement.^{30,31} A study of autologous stem cell transplantation is also ongoing, with favorable anecdotal experience.³²

Conclusion

Dermatologists should participate in the care of patients with systemic sclerosis. They can facilitate patient entry into ongoing trials by aiding in early diagnosis and can also help in the management of specific cutaneous complications such as Raynaud's phenomenon, cutaneous malignancy, and cutaneous calcification. As the puzzle of pathogenesis in sclerotic skin disorders is being unraveled, further promising treatments are certain to become part of our clinical armamentarium.

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are mild and resolve with continued application of the ciclopirox nail lacquer.^{2,6} In the US trials treatment-emergent adverse events, considered by the investigator to be causally related to the test material, were reported in 9% (30/327) of patients applying the ciclopirox nail lacquer and 7% (23/328) of patients using the vehicle. Within each body system the incidence of the adverse events was similar except for the skin and appendages. The incidence in the ciclopirox and vehicle treated groups was 8% and 4%, respectively.²

Drug interaction

Following systemic absorption, ciclopirox is rapidly metabolized by glucuronidation.^{2,6} Ciclopirox is not metabolized through the cytochrome system and no drug interactions are expected.

Dosage and cost

The US package insert recommends that the ciclopirox nail lacquer should be applied evenly over the entire nail plate once daily (preferably at bedtime or 8 hours before washing) to all affected nails with the applicator brush that is provided. If possible, the nail lacquer should be applied to the nail bed, the hyponychium and the ventral surface of the nail plate that is free off the nail bed (i.e., all areas that may be onycholytic). The nail lacquer should be applied daily over the coat that is present from the application of the previous day, with the lacquer film being removed once every 7 days with alcohol. Treatment may need to be continued for 48 weeks and initial improvement of symptoms may not be observed for 26 weeks. Patients are advised not to apply nail polish or other nail cosmetics to the treated nail.

In many of the non-US studies the duration of therapy was 26 weeks and in some cases the frequency of application is less frequent compared to the US studies, e.g., once daily application for 4 weeks and then twice weekly for the next 21 weeks.

Patients should trim the nails weekly and unattached, infected nails should be removed as frequently as monthly by a health care professional trained in the treatment of nail disorders.

Ciclopirox nail lacquer topical solution 8% is supplied in 3.3ml glass bottles, which should be protected from exposure to light. The average wholesale price in the US is \$59.94 USD per bottle.

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Conclusion

Ciclopirox nail lacquer is the first topical nail lacquer to be approved in the US for the treatment of mild to moderate onychomycosis of the fingers and toes, without lunula involvement, due to *Trichophyton rubrum*. The lacquer should be used as a component of a comprehensive management program for onychomycosis involving the patient and a health care professional. In the 2 US pivotal studies the mycological cure rates for ciclopirox 8% nail lacquer and placebo were 34% and 10%, respectively (p<0.001). In studies conducted outside the US efficacy rates were higher, with a meta-analytic average mycological cure rate of 53% when studies conducted worldwide were evaluated as a group. Ciclopirox has a broad spectrum of activity, including *Candida* species and some non-dermatophyte moulds. It remains to be seen to what extent ciclopirox nail lacquer will be used for the management of onychomycosis and whether there will be a paradigm shift in the direction of topical treatment for certain types of onychomycosis.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Scalp Dermatoses	Clobetasol propionate <i>Olux</i> Foam 0.05% Connetics	The US FDA approved this novel foam formulation in May 2000, for the short-term topical treatment of the inflammatory and pruritic manifestations of moderate-to-severe corticosteroid-responsive dermatoses of the scalp.
Oncologic Agent	Alitretinoin 0.1% gel <i>Panretin</i> Ligand Pharmaceuticals	The European Union's Committee for Proprietary Medicinal Products recommended marketing approval in July 2000, of this topical treatment for cutaneous lesions from AIDS-related Kaposi's sarcoma.
Wound Care	Graftskin <i>Apligraf</i> Novartis Pharmaceuticals	The US FDA approved this bi-layered, living skin substitute in June 2000, for expanded use with conventional diabetic foot ulcer care in the treatment of diabetic foot ulcers > 3 weeks in duration.
Oncologic Agent	Bexarotene 1% gel <i>Targretin</i> Ligand Pharmaceuticals	The US FDA approved this gel in June 2000, for the treatment of cutaneous lesions in patients with early-stage cutaneous T-cell lymphoma who cannot tolerate other therapies.
Antiviral Agent	10% Docosanol Cream Avanir Pharmaceuticals	The US FDA issued an approvable letter in June 2000, for the treatment of oral facial herpes. Docosanol is the first approvable OTC treatment for this disease.
Oncologic Agent	Bleomycin <i>ANDA</i> Gensia Sicor Pharmaceuticals	The US FDA tentatively approved Gensia Sicor Pharmaceuticals' <i>ANDA</i> in June 2000, for the generic injection form of Bristol-Myers Squibb's bleomycin (<i>Blenoxane</i>). If fully approved, bleomycin will be used alone or in combination with other chemotherapeutic agents for the management of squamous cell carcinoma, lymphomas and testicular carcinoma.
Drug News		
Oncologic Agent Re: M-Vax	<i>M-Vax</i> (AVAX Technologies), an autologous cancer vaccine for melanoma is now commercially available in Australia for Stage III melanoma metastatic to the lymph node.	
Anorectal Preparations Re: Rectogesic	Cellegy Pharmaceuticals completed the acquisition of Quay Pharmaceuticals in Australia in June 2000. Quay's product <i>Rectogesic</i> (nitroglycerin ointment) for the treatment of anal fissures has been on the market for more than a year in Australia.	
Oncologic Agent Re: <i>Allovectin 7</i>	Phase II and Phase III trials of <i>Allovectin-7</i> (Vical, Inc) will continue on the recommendation of Vical's data safety review board. Phase II studies will evaluate the drug's efficacy in metastatic, refractory stage III or IV melanoma that has not spread to multiple organs. Phase III studies will evaluate this drug with standard chemotherapy in patients with unresectable, metastatic melanoma not previously treated with chemotherapy.	
HIV/AIDS Re: Drug pricing	In an attempt to provide greater access to HIV/AIDS treatment, five pharmaceutical companies will reduce the prices of their drugs to treat HIV and AIDS associated illnesses for South Africa and other developing countries. Participating companies include: Boehringer Ingelheim, F. Hoffman-La Roche, Glaxo Wellcome, Bristol-Myers Squibb, and Merck. The companies are working in cooperation with the United Nations.	
Oncologic Agent Re: Maxamine	The University of Pittsburgh Cancer Institute has reported that the immunomodulating agent <i>Maxamine</i> (histamine dihydrochloride), used in combination with interleukin-2 (IL-2), improved survival for stage IV malignant melanoma patients when compared to those treated with IL-2 alone. Preliminary results also indicated that treatment with <i>Maxamine</i> and IL-2 was safe and well tolerated and had substantially less toxicity than the high-dose regimens of IL-2.	
Urticaria Re: Allegra	In June 2000 Aventis Pharmaceuticals announced that <i>Allegra</i> (fexofenadine HCl) 30mg tablets are now available by prescription for the relief of seasonal allergic rhinitis and chronic idiopathic urticaria in children aged 6-11 years. The US FDA approved <i>Allegra</i> for this additional indication in February 2000.	

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