

Antifungals, Topical Review

02/04/2010

Copyright © 2003 - 2010 by Provider Synergies, L.L.C. All rights reserved.
Printed in the United States of America.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage and retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

*Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Rd. Ste 201
Cincinnati, Ohio 45242*

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.



Together, we can do more.

Antifungals, Topical Review

FDA-Approved Indications

Drug	Tinea pedis	Tinea cruris	Tinea versicolor	Tinea corporis	Cutaneous candidiasis	Other
benzoic acid/ salicylic acid (Bensal HP®) ¹	--	--	--	--	--	Inflammation and irritation associated with common forms of dermatitis Treatment of insect bites, burns and fungal infections
butenafine (Mentax®) ²	X	X	X	X	--	--
ciclopirox (Loprox®) ^{3,4,5,6}	X	X	X	X	X	Seborrheic scalp dermatitis
ciclopirox (Penlac®) ⁷	--	--	--	--	--	Topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails due to <i>Trichophyton rubrum</i>
ciclopirox (CNL-8™) ⁸						
clotrimazole (Lotrimin®) ⁹	X	X	X	X	X	--
clotrimazole / betamethasone (Lotrisone®) ¹⁰	X	X	--	X	X	--
econazole (Spectazole®) ¹¹	X	X	X	X	X	--
ketoconazole (Extina®) ¹²	--	--	--	--	--	Seborrheic dermatitis
ketoconazole cream ¹³	X	X	X	X	X	Seborrheic dermatitis
ketoconazole (Nizoral Shampoo®) ¹⁴	--	--	X	--	--	--
ketoconazole (Xolegel®) ¹⁵	--	--	--	--	--	Seborrheic dermatitis
miconazole (Monistat®, Micatin®) ¹⁶	X	X	X	X	X	--
miconazole / zinc oxide / white petrolatum (Vusion®) ¹⁷	--	--	--	--	--	Diaper dermatitis (adjunctive treatment)
naftifine (Naftin®) ¹⁸	X	X	--	X	--	--
nystatin (Mycostatin®) ¹⁹	--	--	--	--	X	--
nystatin / triamcinolone (Mycolog® II) ²⁰	--	--	--	--	X	--
oxiconazole (Oxistat®) ²¹	X	X	X	X	--	--
sertaconazole (Ertaczo®) ²²	X	--	--	--	--	--
sulconazole (Exelderm®) ²³	X	X	X	X	--	--
terbinafine (Lamisil®) ²⁴	X	X	X	X	--	--
tolnaftate (Tinactin®) ²⁵	X	X	X	X	--	--

Treatment of tinea versicolor requires a legend topical product while the treatment of tinea pedis, tinea cruris, or tinea corporis may be treated with an over-the-counter topical agent.

Drug	Manufacturer
benzoic acid/salicylic acid (Bensal HP)	Seven Oaks
butenafine (Mentax)	Mylan Pharmaceuticals
butenafine OTC	generic
ciclopirox (CNL-8)	JSJ Pharmaceuticals
ciclopirox (Loprox)	generic
ciclopirox (Penlac)	generic
clotrimazole (Lotrimin)	generic
clotrimazole OTC	generic
clotrimazole/betamethasone (Lotrisone)	generic
econazole (Spectazole)	generic
ketoconazole (Extina)	GSK
ketoconazole cream	generic
ketoconazole (Nizoral Shampoo)	generic
ketoconazole (Xolegel)	GSK
miconazole (Monistat, Micatin) OTC	generic
miconazole/zinc oxide/ white petrolatum (Vusion)	GSK
naftifine (Naftin)	Merz
nystatin (Mycostatin)	generic
nystatin/triamcinolone (Mycolog II)	generic
oxiconazole (Oxistat)	PharmaDerm
sertaconazole (Ertaczo)	OMJPI
sulconazole (Exelderm)	Ranbaxy
terbinafine (Lamisil) OTC	generic
tolnaftate OTC	generic

Overview

Tinea cruris, corporis, and pedis, named for the body sites involved, are superficial fungal infections (dermatophytosis) caused by three genera of dermatophytes: *Trichophyton*, *Microsporum*, and *Epidermophyton*.²⁶ These dermatophytes are a homogenous group of fungi that live on the keratin of the stratum corneum, nails, and hair. The estimated lifetime risk of acquiring tinea infections is between ten and 20 percent.²⁷

Dryness of the skin's outer layer discourages colonization by microorganisms, and shedding of epidermal cells keeps many microbes from establishing residence. With inhibition or failure of the skin's protective mechanisms, cutaneous infection may occur with subsequent pruritus, redness, and scaling. Since dermatophytes require keratin for growth, they are restricted to hair, nails, and superficial skin; therefore, most can be treated with topical antifungal medications.²⁸

Tinea pedis (athlete's foot) is one of the most common superficial fungal infections of the skin and is most often caused by the dermatophytes *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.²⁹ Affected skin is usually pruritic with scaling plaques on the soles extending to the lateral aspect of the feet and interdigital spaces. Tinea cruris is a dermatophyte infection of the groin (jock itch) also caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*. This condition affects the skin of the medial and upper parts of the thighs, usually bilaterally, with severe pruritis. Tinea corporis (ringworm on the skin) refers to tinea anywhere on the body except the scalp, beard, feet, or hands. *Trichophyton* and *Microsporum* are usually the causative organisms. Each lesion may have one or several concentric rings with red papules or plaques in the center. As the lesion progresses, the center may clear, leaving post-inflammatory hypopigmentation or hyperpigmentation.

Tinea versicolor, a common superficial fungal infection, is caused by *Malassezia* species (formerly *Pityrosporon*).³⁰ This organism is part of the normal flora in most individuals but is capable of becoming pathogenic under certain conditions. The most distinctive clinical feature is the change in pigmentation on the affected sites. Mild scaling and pruritis are usually the only other sequelae.

Cutaneous candidiasis, usually caused by *Candida albicans*, may colonize occluded areas or folds of the skin, producing infection in areas such as the groin, axillae, and interdigital spaces. Clinical manifestations include erythema, scaling, maceration, vesicles, and pustules.

Onychomycosis is a fungal infection of the nailbed (skin beneath the nail plate) with secondary involvement of the nailplate (visible part of the nail on fingers and toes). The main pathogens responsible for onychomycosis are dermatophytes, yeasts, and molds. Despite significant improvements, approximately 20 percent of patients with onychomycosis still fail on antifungal therapy. More common in toenails than fingernails, they often cause the end of the nail to separate from the nail bed. Additionally, debris (white, green, yellow, or black) may build up under the nail plate and discolor the nail bed.³¹

Seborrheic dermatitis is one of the more common cutaneous diseases.³² One proposed etiology is overgrowth of yeast, which normally inhabits sebaceous skin of the scalp, eyebrows, and central face. The disease typically occurs in three age groups, which are infancy, middle age, and seniors. Seborrheic dermatitis in adults typically involves the scalp, face, neck, mid upper chest, and intertriginous zones (axillae, groin, and submammary).

Pharmacology³³

The mechanism of action of benzoic acid/salicylic acid (Bensal HP) is unknown. It has been demonstrated that benzoic acid/salicylic acid (Bensal HP) reduces methicillin-resistant *Staphylococcus aureus* (MRSA) protected by biofilms in wounds using porcine models and stimulates re-epithelialization of second-degree burns in porcine models.

The other agents in this category can be divided into two principal pharmacologic antifungal groups, the allylamines and the azoles.

Butenafine (Mentax) is structurally and pharmacologically related to the allylamine antifungal agents, which include naftifine (Naftin) and terbinafine (Lamisil). The exact mechanisms of the fungicidal action are unknown for these agents. Presumably, they exert antifungal activity by altering cellular membranes resulting in increased cellular permeability and growth inhibition. They may also interfere with sterol biosynthesis at an earlier stage than do the imidazole derivatives. They are active against many fungi and yeasts. Tolnaftate (Tinactin) works in a similar manner to these agents, although it is a thiocarbamate antifungal. Shorter time to cure is usually seen with fungicidal agents.

Clotrimazole (Lotrimin), econazole (Spectazole), ketoconazole (Extina, Xolegel), miconazole (Monistat, Vusion), oxiconazole (Oxistat), sulconazole (Exelderm), and sertaconazole (Ertaczo) are azole antifungals (imidazole derivatives). The imidazole-derivative azole antifungals exert antifungal activity by altering cell membrane permeability by binding with phospholipids in the fungal cell membrane. They are active against many fungi including dermatophytes and yeasts. The azole antifungals, miconazole, clotrimazole, and ketoconazole are fungistatic and generally require epidermal turnover to shed living fungus from the skin.³⁴

Ciclopirox (Loprox, Penlac, CNL-8) is thought to act by chelating polyvalent cations (Fe^{+3} or Al^{+3}) resulting in the inhibition of the metal dependent enzymes responsible for the degradation of peroxides within the fungal cell. Ciclopirox is active against many genera of fungi including dermatophytes and yeast.

Nystatin (Mycostatin) exerts its antifungal activity by binding to sterols in the fungal cell membrane. As a result of this binding, the membrane is no longer able to function as a selective barrier, and potassium and other cellular constituents are lost.

Pharmacokinetics^{35,36,37,38,39,40,41,42,43,44,45,46,47,48}

Due to the nature of topical application, all products minimally expose the systemic circulation.

Cream: Creams are oil-in-water emulsions and are generally less greasy than ointments. Creams are usually less effective than ointments.

Gel: Gels consist of a solid, jelly-like material that is mostly liquid, but contains a substantially dilute crosslinked system that gives the gel the property of thixotropy (the gel is solid until the material is agitated and then becomes liquid). They can also be a highly absorbent drug delivery system with natural or synthetic polymers, and can act as reservoirs in topical drug delivery.

Lotion: Lotions are diluted creams.

Ointment: Ointments are best at delivering drug to the skin and provide a barrier.

Solutions: Solutions are typically alcoholic liquids and are especially useful for the scalp because they do not coat the hair.

Lacquer: Nail lacquers are topical solutions intended only for use on fingernails and toenails and immediately adjacent skin.

Foam: Foam is a topical product that can be used on the scalp, body, and face. It quickly dissolves leaving minimal residue.

Powder: Powders are beneficial due to their ease of application but generally are less effective than other formulations. Due to their lack of absorption, they can be used over large areas and sometimes are used preventatively in patients prone to tinea pedis and tinea cruris.

Contraindications/Warnings

Hypersensitivity to any component of these agents is considered a contraindication for use.⁴⁹ These are topical agents and not intended for ophthalmic, vaginal, or oral use.⁵⁰

Benzoic acid/salicylic acid (Bensal HP) is contraindicated in patients with hypersensitivity type reactions to topical polyethylene glycols.⁵¹

Ciclopirox (Loprox, Penlac, CNL-8) should be avoided in patients with a history of seizure disorders or immunosuppression.^{52,53,54}

Combination products containing corticosteroids (Lotrisone, Mycolog II) can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression if applied over large surface areas, associated with prolonged use, used under occlusive dressings, or used in combination with other topical corticosteroids. If HPA suppression is noted, then if possible, the drug should be discontinued or the application reduced in frequency.^{55,56}

Xolegel contains 34 percent dehydrated alcohol so fire, flame, or smoking during and immediately following application of Xolegel should be avoided.⁵⁷

Effects such as hepatitis, lowered testosterone and ACTH induced corticosteroid serum levels have been seen with oral ketoconazole; however, these adverse events have not been observed with topical ketoconazole.⁵⁸

Loprox shampoo has had some rare reports of hair discoloration occurring on patients with light colored hair.⁵⁹

Drug Interactions⁶⁰

Significant drug interactions with the topical agents have not been noted.

Adverse Effects

Drug	Burning	Itching	Application Site Reaction	Erythema
benzoic acid/salicylic acid (Bensal HP) ⁶¹	reported	nr	nr	nr
butenafine (Mentax) ⁶²	<2	<2	<2	<2
ciclopirox (Loprox) ^{63,64,65,66}	7-34	1-5	1-5	nr
ciclopirox (Penlac, CNL-8) ^{67,68}	1	nr	1	5
clotrimazole (Lotrimin) ⁶⁹	reported	reported	reported	reported
clotrimazole/betamethasone (Lotrisone) ⁷⁰	reported	reported	reported	reported
econazole (Spectazole) ⁷¹	reported	reported	3	reported
ketoconazole (Extina) ⁷²	10	<1	6	<1
ketoconazole cream ⁷³	5	reported	reported	nr
ketoconazole (Nizoral Shampoo) ⁷⁴	nr	<3	<3	nr
ketoconazole (Xolegel) ⁷⁵	4	<1	reported	<1
miconazole (Monistat, Micatin) ⁷⁶	reported	reported	reported	nr
miconazole/zinc oxide/white petrolatum (Vusion) ⁷⁷	nr	nr	reported	nr
naftifine (Naftin) ⁷⁸	5-6	1-2	2	0.5-2
nystatin (Mycostatin) ⁷⁹	nr	nr	reported	nr
nystatin/ triamcinolone (Mycolog II) ⁸⁰	reported	reported	reported	nr
oxiconazole (Oxistat) ⁸¹	0.7-1.4	0.4-1.6	0.4	0.2
sertaconazole (Ertaczo) ⁸²	reported	nr	reported	nr
sulconazole (Exelderm) ⁸³	3	3	reported	1
terbinafine (Lamisil) ⁸⁴	1-2	1-2	1-2	nr
tolnaftate (Tinactin) ⁸⁵	nr	nr	reported	nr

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative. nr = not reported

The incidence of nail disorders, such as shape change, irritation, ingrown toenail, discoloration, and application site reactions were similar between ciclopirox (Penlac, CNL-8) and vehicle.

Special PopulationsPediatrics

Fungal infections can occur in children and may frequently present as tinea corporis (includes ringworm), diaper dermatitis, and tinea capitis. Infants and young children may experience diaper dermatitis when infected with *Candida* sp., which may respond rapidly to topical therapy including ciclopirox, nystatin, and several other agents in this class.⁸⁶ Drugs which have safety and effectiveness data for children include clotrimazole, miconazole, and tolnaftate which can be used in patients ages two years and older; Vusion may be used in children four weeks and

Antifungals, Topical

older.⁸⁷ In addition, butenafine (Mentax), ketoconazole gel (Xolegel), ketoconazole foam (Extina), and sertaconazole (Ertaczo) are approved for use in children ages 12 years and older.⁸⁸ Oxiconazole (Oxistat) cream may be used in pediatric patients for tinea corporis, tinea cruris, tinea pedis, and tinea versicolor; however, these approved indications rarely occur in children less than the age of 12 years. Ciclopirox cream and suspension can be used in patients aged 10 years and older, nail lacquer in patients aged 12 years and older, and gel and shampoo in patients aged 16 years and older. Nystatin can be used at any age including infancy, while the combination product nystatin/triamcinolone can be used in children two months of age and older. Clotrimazole/betamethasone is not recommended for those less than 17 years of age.⁸⁹ Safety and effectiveness of econazole (Spectazole), ketoconazole cream, naftifine (Naftin), sulconazole (Exelderm) and terbinafine (Lamisil) for pediatric patients have not been established.^{90,91,92}

Pregnancy⁹³

All agents in this category are Pregnancy Category B with the exception of benzoic acid/salicylic acid (Bensal HP), clotrimazole/betamethasone, econazole (Spectazole), ketoconazole, miconazole, nystatin, nystatin/triamcinolone, sertaconazole (Ertaczo), sulconazole (Exelderm), and tolnaftate, which are Pregnancy Category C.

Dosages

Drug	Frequency of Application	Rx Availability	OTC Availability
benzoic acid/salicylic acid (Bensal HP) ⁹⁴	Twice daily for seven days	6%/3% ointment	--
butenafine (Mentax) ⁹⁵	Once to twice daily for one to four weeks	1% cream	Lotrimin Ultra 1% cream
ciclopirox (Loprox) ^{96,97,98,99}	Cream, gel, topical suspension: twice daily for four weeks Shampoo: Apply 5 mL to scalp as directed twice a week for four weeks; a minimum of three days should occur between applications	0.77% cream 0.77% gel 0.77% TS suspension 1% shampoo	--
ciclopirox (Penlac) ¹⁰⁰	Once daily (preferably at bedtime or eight hours before washing) to all affected nails for 48 weeks; daily applications should be made over the previous coat and removed with alcohol every seven days	8% nail lacquer topical solution	--
ciclopirox (CNL-8) ¹⁰¹			
clotrimazole (Lotrimin) ¹⁰²	Two to four times daily for up to four weeks	1% cream 1% solution	AF 1% cream AF 1% lotion AF 1% solution
clotrimazole / betamethasone (Lotrisone) ¹⁰³	Twice daily for two to four weeks	1% / 0.05% cream 1% / 0.05% lotion	--
econazole (Spectazole) ¹⁰⁴	Once to twice daily for two to four weeks	1% cream	--
ketoconazole (Extina) ¹⁰⁵	Twice daily for four weeks	2% foam	--
ketoconazole cream ¹⁰⁶	Cream: once daily for two to six weeks depending on indication; apply twice daily for four weeks or until clinical clearing for seborrheic dermatitis	2% cream	--

Dosages (continued)

Drug	Frequency of Application	Rx Availability	OTC Availability
ketoconazole (Nizoral Shampoo) ¹⁰⁷	Shampoo 2%: use as directed twice a week for four weeks Shampoo 1%: use every three to four days for up to eight weeks	2% cream 2% shampoo	A-D 1% shampoo
ketoconazole (Xolegel) ¹⁰⁸	Daily for two weeks	2% gel	--
miconazole (Monistat, Micatin) ¹⁰⁹	Twice daily for two to four weeks	2% cream	2% cream 2% powder 2% liquid 2% spray
miconazole / zinc oxide / white petrolatum (Vusion) ¹¹⁰	Apply at each diaper change for seven days	0.25% / 15% / 81.35% ointment	--
naftifine (Naftin) ¹¹¹	Cream: daily for four weeks Gel: twice daily for four weeks	1% cream 1% gel	--
nystatin (Mycostatin) ¹¹²	Cream, ointment: twice daily until healing is complete Powder: two to three times daily until healing is complete	100,000 units / gm cream 100,000 units / gm powder 100,000 units / gm ointment	--
nystatin / triamcinolone ¹¹³	Twice daily	100,000 units / gm / 0.1% cream 100,000 units / gm / 0.1% ointment	--
oxiconazole (Oxistat) ¹¹⁴	Once to twice daily for two to four weeks	1% cream 1% lotion	--
sertaconazole (Ertaczo) ¹¹⁵	Twice daily for four weeks	2% cream	--
sulconazole (Exelderm) ¹¹⁶	Once to twice daily for two to four weeks	1% cream 1% solution	
terbinafine (Lamisil) ¹¹⁷	Solution: twice daily for one week Cream: twice daily for one to two weeks Spray: once or twice daily for one week Gel: once daily for one week	--	1% cream 1% spray 1% gel
tolnaftate (Tinactin) ¹¹⁸	Twice daily for two to four weeks	--	1% cream 1% powder 1% powder spray 1% solution 1% gel 1% liquid spray

In general, tinea corporis and tinea cruris require treatment for two weeks whereas tinea pedis may require treatment for up to four weeks.¹¹⁹ Treatment should continue for at least one week after symptoms have resolved.¹²⁰ Therapy with ciclopirox (Penlac, CNL-8) is recommended for 48 weeks.

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved topical use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Tinea Cruris and Tinea Corporis:

butenafine (Mentax) versus clotrimazole (Lotrimin)

Eighty patients, diagnosed with tinea cruris or tinea corporis, were randomly assigned to butenafine once daily for two weeks or clotrimazole twice daily for four weeks in a double-blind manner.¹²¹ Follow-up was done at one, two, four, and eight weeks. At the end of one week, butenafine recipients exhibited higher clinical cure rate compared to clotrimazole recipients (26.5 versus 2.9 percent) as well as higher mycological cure (61.7 versus 17.6 percent); however, this difference was not statistically significant at four and eight weeks of treatment.

naftifine (Naftin) versus econazole (Spectazole)

Patients with tinea cruris or tinea corporis (n=104) were evaluated in a double-blind, randomized study.¹²² Naftifine 1% cream or econazole 1% cream were applied to affected areas twice daily for four weeks. After one week of treatment, naftifine had an overall cure rate of 19 percent compared with four percent for econazole (p=0.03). Two weeks after the end of treatment, both medications had overall cure rates of approximately 80 percent. A difference in favor of naftifine, although not statistically significant after the first week, persisted throughout treatment. Three percent of the naftifine patients had adverse effects compared with 13 percent of the econazole subjects.

Tinea Pedis:

ketoconazole (Nizoral) versus clotrimazole (Lotrimin)

The effects of clotrimazole 1% cream and ketoconazole 2% cream were compared in a double-blind, randomized manner for therapy of interdigital tinea pedis in 106 treated patients.¹²³ Ketoconazole cream was used twice daily, and clotrimazole cream was administered once daily; both used for four weeks. The number of patients with cure or improvement after four weeks was comparable (62 percent clotrimazole group versus 64 percent ketoconazole group). The mycological response revealed a negative culture and microscopy in 53.1 versus 52.1 percent of the patients after 14 days, in 76 versus 79.2 percent after 28 days, and in 83.7 versus 76.9 percent after 56 days of observation in clotrimazole versus ketoconazole, respectively. The overall score of the development of tinea-related signs and symptoms did not show relevant differences between the two drugs. Better results were obtained under clotrimazole than under

ketoconazole for pruritus (97.8 versus 89.6 percent) and burning/stinging (97.5 versus 89.4 percent). Treatments appeared comparably safe and tolerable.

terbinafine (Lamisil) versus clotrimazole (Lotrimin)

A multicenter, randomized, double-blind, parallel-group study in 256 patients with tinea pedis compared the safety and efficacy of the twice daily application of terbinafine 1% cream for one week (placebo given for the remaining three weeks) with the twice daily application of clotrimazole 1% cream for four weeks.¹²⁴ Mycological cure and effective treatment were assessed four and six weeks after commencing therapy. Mycological cure rates at four weeks were 93.5 percent for terbinafine and 73.1 percent for clotrimazole ($p=0.0001$). Effective treatment rates at four weeks were 89.7 percent for terbinafine and 58.7 percent for clotrimazole ($p=0.0001$), and at six weeks 89.7 percent for terbinafine and 73.1 percent for clotrimazole ($p=0.002$).

In a double-blind, clinical trial, 429 tinea pedis patients were randomized to receive terbinafine 1% topical solution twice daily for one week followed by a vehicle application for three weeks, or clotrimazole 1% solution for four weeks.¹²⁵ Patients were evaluated at baseline and at weeks one, two, four (end of treatment), and eight (end of follow-up). Effective treatment results were similar and were recorded in 83 percent of terbinafine patients and 82 percent of clotrimazole patients. Mycological cure and disappearance of signs and symptoms were similar at each assessment visit in the two groups. The mycological cure rate was 95 percent with terbinafine solution and 91 percent with clotrimazole solution ($p=0.05$). Mild to moderate adverse events occurred in four to five percent of patients in each group.

A multicenter, prospective, randomized, double-blind, parallel-group study compared the efficacy and tolerability of terbinafine 1% cream with clotrimazole 1% cream in the treatment of interdigital tinea pedis.¹²⁶ Patients received either terbinafine twice daily for one week followed by a placebo cream for five weeks or clotrimazole twice daily for four weeks. Outcome measures were observed at one, four, eight, and 12 weeks after the commencement of the study. Of the 217 patients randomized, 104 had a culture-confirmed dermatophyte infection at baseline. In these patients, 84.6 percent in the terbinafine group were culture-negative after one week compared with only 55.8 percent in the clotrimazole group. Both agents were well tolerated.

sertaconazole (Ertaczo) versus placebo

A total of 383 patients with tinea pedis were evaluated after receiving either sertaconazole 2% cream twice daily for four weeks or vehicle control in two randomized, double-blind, parallel group, multicenter studies.¹²⁷ Results demonstrated a 70.3 percent mycologic cure reported in the study group versus 36.7 percent with the vehicle group ($p<0.0001$). At week six, 46.7 percent of the sertaconazole group had successful treatment outcomes versus 14.9 percent of the vehicle group ($p<0.0001$). Both treatment arms were well-tolerated.

Tinea Versicolor:

ciclopirox cream (Loprox) versus clotrimazole cream

Two randomized, double-blind, parallel-group, multicenter studies assessed the efficacy and safety of ciclopirox 1% cream in patients with tinea versicolor.¹²⁸ The first study compared ciclopirox with the placebo cream vehicle, and the second study compared ciclopirox 1% cream to clotrimazole 1% cream. In both studies, treatments were applied topically twice a day for 14

days. Clinical and mycological cure responses were compared at treatment weeks one and two, and then post-treatment weeks one and two. Results from the first study demonstrated 49 percent of the ciclopirox treatment group (n=73) were clinically and mycologically cured after two weeks versus 24 percent of the placebo treatment group (n=72; p<0.001). Results from the second study demonstrated that 77 percent of the patients treated with ciclopirox cream were clinically and mycologically cured after two weeks of treatment versus 45 percent of patients treated with clotrimazole cream (p<0.001). Two weeks post-treatment, the proportion of patients with combined response was slightly greater in the ciclopirox treatment group versus the clotrimazole treatment group (86 percent versus 73 percent, respectively). No adverse effects were observed in either group.

sulconazole (Exelderm) versus miconazole (Monistat)

Sulconazole 1% cream and miconazole 2% cream were compared in the treatment of tinea versicolor in a double-blind, multicenter, randomized clinical trial enrolling 192 patients.¹²⁹ The medications were applied twice daily for three weeks. Of 181 patients analyzed for efficacy at the end of the treatment trial, 93 percent of the sulconazole patients and 87 percent of miconazole patients became KOH-negative. The complete clearing of tinea versicolor lesions occurred in 89 percent of sulconazole-treated patients and 82 percent of miconazole-treated patients. Cutaneous adverse effects, predominantly transient itching, were reported in eight patients receiving sulconazole and in four patients receiving miconazole. No systemic adverse events were reported.

Onychomycosis:

ciclopirox (Penlac) versus placebo

Two double-blind, vehicle-controlled multicenter studies were performed in the United States to evaluate the use of ciclopirox 8% nail lacquer to treat mild to moderate toenail onychomycosis caused by dermatophytes.¹³⁰ A total of 460 patients were randomized to ciclopirox (n=231) or vehicle (n=229). Treatment was applied daily for 48 weeks. At the end of the 48-week treatment period, the mycologic cure rate in study I was 29 percent for ciclopirox and 11 percent for the vehicle group. In study II, mycologic cure rates were 36 and nine percent, respectively. The most common adverse reactions were transient and localized to the site of action (e.g., erythema and application site reaction).

Seborrheic Dermatitis:

ketoconazole foam (Extina) versus ketoconazole cream

A total of 1,162 subjects, aged 12 years or older, with mild to severe seborrheic dermatitis were randomized to receive ketoconazole foam (n=427), vehicle foam (n=420), ketoconazole cream (n=210), or vehicle cream (n=105) twice daily for four weeks.¹³¹ The primary endpoint was the proportion of subjects achieving an Investigator's Static Global Assessment score of 0 or 1 at week four (treatment success). A significantly greater percentage of subjects achieved treatment success using ketoconazole foam than vehicle foam (56 percent and 42 percent, respectively; p<0.0001). Ketoconazole foam was well-tolerated with a low incidence of treatment-related adverse events (14 percent). Ketoconazole foam was shown to be equivalent to ketoconazole cream.

ketoconazole gel (Xolegel) versus vehicle

A randomized phase 3, vehicle-controlled trial was performed on 459 people to evaluate the efficacy of ketoconazole 2% gel in comparison to the vehicle after two weeks of treatment in moderate to severe seborrheic dermatitis.¹³² The primary endpoint was to evaluate the proportion of patients who had either cleared or almost cleared dermatitis after 28 days. Results indicated that 25.3 percent of patients treated with ketoconazole 2% gel experienced successful treatment in comparison to 13.9 percent of patients receiving the vehicle alone (p=0.0014). In addition, ketoconazole 2% gel helped to improve erythema, scaling, and pruritis when compared to the vehicle (p=0.0022). Few adverse events were reported, but the adverse events that were experienced were mild and moderate and similar between both groups.

Two studies compared the effectiveness of a combination gel containing ketoconazole 2% and desonide 0.05%, each active gel individually, and a vehicle control in patients with moderate to severe seborrheic dermatitis.¹³³ The primary endpoint was efficacy measured by the proportion of patients who experienced an improvement in scaling and erythema as well as the investigator global assessment scores. A score of 0 or 1, if the baseline was ≥ 3 , defined effective treatment in these patients after 28 days. The comparison of the combination gel to its individual components revealed that the efficacy of ketoconazole alone was comparable to the combination gel as well as desonide gel alone for up to two weeks after the end of treatment.

Meta-Analysis

Recent systematic review was conducted to evaluate topical treatments for fungal infections of the skin and nails of the foot.¹³⁴ Authors searched the Cochrane Skin Group Specialized Register (January 2005), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 1, 2005), MEDLINE and EMBASE (from inception to January 2005). The study objectives were to assess the effects of topical treatments in successfully treating fungal infections of the skin of the feet and toenails and in preventing recurrence. In conclusion, allylamines and azoles for athlete's foot consistently produce a much higher percentage of cures than placebo. Allylamines cure slightly more infections than azoles and are now available over-the-counter.

Summary

Many topical antifungal preparations are available as prescription medications and over-the-counter (OTC) products. Limited data are available regarding comparative efficacy in the treatment of the various fungal infections - tinea cruris, tinea corporis, tinea pedis, and tinea versicolor. In general, tinea corporis and tinea cruris require treatment for two weeks, and tinea pedis may require treatment for four weeks. Treatment should continue for at least one week after symptoms have resolved. Combination therapy (antifungal plus corticosteroid) can be considered when inflammation is present. The safety of the topical agents is inherently limited to local exposure.

Limited data are also lacking in comparative efficacy for the treatment of the skin condition, seborrheic dermatitis. Both ciclopirox (Loprox) and ketoconazole (Extina, Xolegel) have been approved for use in this condition, but superiority has not been established for either agent due to the lack of well designed comparative clinical studies.

Due to the lack of comparative studies with ciclopirox (Penlac, CNL-8) for the treatment of onychomycosis, it is difficult to measure its effectiveness versus other indicated products. An oral antifungal, if tolerated, may lead to higher success rates in the treatment of onychomycosis.

The combination product miconazole, zinc oxide, and white petrolatum (Vusion) is indicated as adjunctive treatment for diaper dermatitis in patients four weeks and older. The other agents with safety and effectiveness data for children ages two years and older are clotrimazole, miconazole, and tolnaftate.

Based on the limited amount of efficacy data available for these various agents in the treatment of dermatologic fungal infections, choice of therapy is mainly based on clinical judgment with regard to prior treatments and complicating conditions such as bacterial growth or intense inflammation.

References

- ¹ Bensal HP [package insert]. Greenville, SC; HS Pharma; February 2009.
- ² Available at: <http://www.clinicalpharmacology.com>. Accessed February 2, 2010.
- ³ Loprox gel [package insert]. Scottsdale, AZ; Medicis Derm; July 2005.
- ⁴ Loprox cream [package insert]. Scottsdale, AZ; Medicis Derm; March 2003.
- ⁵ Loprox topical solution [package insert]. Scottsdale, AZ; Medicis Derm; May 2003.
- ⁶ Loprox shampoo [package insert]. Scottsdale, AZ; Medicis Derm; September 2008.
- ⁷ Penlac nail lacquer [package insert]. Bridgewater, NJ; Dermik Laboratories; July 2006.
- ⁸ CNL-8 [package insert]. Charleston, SC; JSJ Pharmaceuticals; December 2007.
- ⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹¹ Econazole. Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹³ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁴ Nizoral 2% Shampoo [package insert]. Raritan, NJ; PriCara; January 2009.
- ¹⁵ Xolegel [package insert]. Coral Gables, FL; Stiefel Laboratories, Inc.; January 2010.
- ¹⁶ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁷ Vusion [package insert]. Princeton, NJ; Barrier Therapeutics; September 2007.
- ¹⁸ Naftin [package insert]. Greensboro, NC; Merz Pharmaceuticals; February 2009.
- ¹⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ²⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ²¹ Oxistat [package insert]. Melville, NY; Pharmaderm, a division of Nycomed US Inc; March 2008.
- ²² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ²³ Exelderm [package insert]. Jacksonville, FL; Ranbaxy; September 2007.
- ²⁴ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ²⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ²⁶ Weitzman I, Summerbell RC. The dermatophytes. Clin Microbiol Rev. 1995; 8:240-59.
- ²⁷ Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. J Am Acad Dermatol. 1996; 34(2 pt 1):282-6.
- ²⁸ Gupta AK, Einarson TR, Summerbell RC, et al. An overview of topical antifungal therapy in dermatomycoses. A North American perspective. Drugs. 1998; 55:645-74.
- ²⁹ Leyden JL. Tinea pedis: pathophysiology and treatment. J Am Acad Dermatol. 1994; 31 (3 Pt 2): S31-S33.
- ³⁰ Schwartz RA. Superficial fungal infections. Lancet. 2004; 364(944):1173-1182.
- ³¹ American Academy of Dermatology website. Available at: <http://www.aad.org/public/Publications/pamphlets/NailFungus.htm>. Accessed February 3, 2010.
- ³² American Academy of Dermatology website. Available at: http://www.aad.org/public/publications/pamphlets/common_seb_dermatitis.html. Accessed February 3, 2010.
- ³³ Available at: <http://www.clinicalpharmacology.com>. Accessed February 2, 2010.
- ³⁴ Kyle AA, Dahl MV. Topical therapy for fungal infections. Am J Clin Dermatol. 2004; 5(6):443-51.
- ³⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 2, 2010.
- ³⁶ Loprox gel [package insert]. Scottsdale, AZ; Medicis Derm; July 2005.
- ³⁷ Loprox cream [package insert]. Scottsdale, AZ; Medicis Derm; March 2003.
- ³⁸ Loprox topical solution [package insert]. Scottsdale, AZ; Medicis Derm; May 2003.
- ³⁹ Loprox shampoo [package insert]. Scottsdale, AZ; Medicis Derm; September 2008.
- ⁴⁰ Nizoral 2% Shampoo [package insert]. Raritan, NJ; PriCara; January 2009.
- ⁴¹ Vusion [package insert]. Princeton, NJ; Barrier Therapeutics; September 2007.
- ⁴² Naftin [package insert]. Greensboro, NC; Merz Pharmaceuticals; February 2009.
- ⁴³ Oxistat [package insert]. Melville, NY; Pharmaderm, a division of Nycomed US Inc; March 2008.
- ⁴⁴ Xolegel [package insert]. Coral Gables, FL; Stiefel Laboratories, Inc.; January 2010.

- ⁴⁵ Penlac nail lacquer [package insert]. Bridgewater, NJ; Dermik Laboratories; July 2006.
- ⁴⁶ CNL-8 [package insert]. Charleston, SC; JSJ Pharmaceuticals; December 2007.
- ⁴⁷ Available at: <http://en.wikipedia.org/wiki/Gel>. Accessed February 3, 2010.
- ⁴⁸ Exelderm [package insert]. Jacksonville, FL; Ranbaxy; September 2007.
- ⁴⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁵⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁵¹ Bensal HP [package insert]. Greenville, SC; HS Pharma; February 2009.
- ⁵² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁵³ CNL-8 [package insert]. Charleston, SC; JSJ Pharmaceuticals; December 2007.
- ⁵⁴ Penlac nail lacquer [package insert]. Bridgewater, NJ; Dermik Laboratories; July 2006.
- ⁵⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁵⁶ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁵⁷ Xolegel [package insert]. Coral Gables, FL; Stiefel Laboratories, Inc.; January 2010.
- ⁵⁸ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁵⁹ Loprox shampoo [package insert]. Scottsdale, AZ; Medicis Derm; September 2008.
- ⁶⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁶¹ Bensal HP [package insert]. Greenville, SC; HS Pharma; February 2009.
- ⁶² Available at: <http://www.clinicalpharmacology.com>. Accessed February 2, 2010.
- ⁶³ Loprox gel [package insert]. Scottsdale, AZ; Medicis Derm; July 2005.
- ⁶⁴ Loprox cream [package insert]. Scottsdale, AZ; Medicis Derm; March 2003.
- ⁶⁵ Loprox topical solution [package insert]. Scottsdale, AZ; Medicis Derm; May 2003.
- ⁶⁶ Loprox shampoo [package insert]. Scottsdale, AZ; Medicis Derm; September 2008.
- ⁶⁷ Penlac nail lacquer [package insert]. Bridgewater, NJ; Dermik Laboratories; July 2006.
- ⁶⁸ CNL-8 [package insert]. Charleston, SC; JSJ Pharmaceuticals; December 2007.
- ⁶⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁷⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁷¹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁷² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁷³ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁷⁴ Nizoral 2% Shampoo [package insert]. Raritan, NJ; PriCara; January 2009.
- ⁷⁵ Xolegel [package insert]. Coral Gables, FL; Stiefel Laboratories, Inc.; January 2010.
- ⁷⁶ Available at: <http://www.clinicalpharmacology.com>. February 3, 2010.
- ⁷⁷ Vusion [package insert]. Princeton, NJ; Barrier Therapeutics; September 2007.
- ⁷⁸ Naftin [package insert]. Greensboro, NC; Merz Pharmaceuticals; February 2009.
- ⁷⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁸⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁸¹ Oxistat [package insert]. Melville, NY; Pharmaderm, a division of Nycomed US Inc; March 2008.
- ⁸² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁸³ Exelderm [package insert]. Jacksonville, FL; Ranbaxy; September 2007.
- ⁸⁴ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁸⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁸⁶ Gallup E, Plott T; Ciclopirox TS Investigators. A multicenter, open-label study to assess the safety and efficacy of ciclopirox topical suspension 0.77% in the treatment of diaper dermatitis due to *Candida albicans*. *J Drugs Dermatol*. 2005; 4(1):29-34.
- ⁸⁷ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁸⁸ Available at: <http://www.clinicalpharmacology.com>. Accessed February 2, 2010.
- ⁸⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁹⁰ Exelderm [package insert]. Jacksonville, FL; Ranbaxy; September 2007.
- ⁹¹ Naftin [package insert]. Greensboro, NC; Merz Pharmaceuticals; February 2009.
- ⁹² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁹³ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ⁹⁴ Bensal HP [package insert]. Greenville, SC; HS Pharma; February 2009.
- ⁹⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 2, 2010.
- ⁹⁶ Loprox gel [package insert]. Scottsdale, AZ; Medicis Derm; July 2005.
- ⁹⁷ Loprox cream [package insert]. Scottsdale, AZ; Medicis Derm; March 2003.
- ⁹⁸ Loprox topical solution [package insert]. Scottsdale, AZ; Medicis Derm; May 2003.
- ⁹⁹ Loprox shampoo [package insert]. Scottsdale, AZ; Medicis Derm; September 2008.
- ¹⁰⁰ Penlac nail lacquer [package insert]. Bridgewater, NJ; Dermik Laboratories; July 2006.
- ¹⁰¹ CNL-8 [package insert]. Charleston, SC; JSJ Pharmaceuticals; December 2007.
- ¹⁰² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁰³ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁰⁴ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁰⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁰⁶ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹⁰⁷ Nizoral 2% Shampoo [package insert]. Raritan, NJ; PriCara; January 2009.
- ¹⁰⁸ Xolegel [package insert]. Coral Gables, FL; Stiefel Laboratories, Inc.; January 2010.
- ¹⁰⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.
- ¹¹⁰ Vusion [package insert]. Princeton, NJ; Barrier Therapeutics; September 2007.
- ¹¹¹ Naftin [package insert]. Greensboro, NC; Merz Pharmaceuticals; February 2009.
- ¹¹² Available at: <http://www.clinicalpharmacology.com>. Accessed February 3, 2010.

- ¹¹³ Available at: <http://www.clinicalpharmacology.com> Accessed February 3, 2010.
- ¹¹⁴ Oxistat [package insert]. Melville, NY; Pharmaderm, a division of Nycomed US Inc; March 2008.
- ¹¹⁵ Available at: <http://www.clinicalpharmacology.com> Accessed February 3, 2010.
- ¹¹⁶ Exelderm [package insert]. Jacksonville, FL; Ranbaxy; September 2007.
- ¹¹⁷ Available at: <http://www.clinicalpharmacology.com> Accessed February 3, 2010.
- ¹¹⁸ Available at: <http://www.clinicalpharmacology.com> Accessed February 3, 2010.
- ¹¹⁹ Gupta AK, Einarson TR, Summerbell RC, et al. An overview of topical antifungal therapy in dermatomycoses. A North American perspective. *Drugs*. 1998; 55:645-74.
- ¹²⁰ Fitzpatrick TB, Johnson RA, Wolff K, et al. Cutaneous fungal infections. In: *Color atlas and synopsis of clinical dermatology: common and serious diseases*. Fitzpatrick TB, et al., Eds. 3d ed. New York: McGraw-Hill, 1997:688-733.
- ¹²¹ Singal A, Pandhi D, Agrawal S, et al. Comparative efficacy of topical 1% butenafine and 1% clotrimazole in tinea cruris and tinea corporis: a randomized, double-blind trial. *J Dermatolog Treat*. 2005; 16(5-6):331-335.
- ¹²² Millikan LE, Galen WK, Gewirtzman GB, et al. Naftifine cream 1% versus econazole cream 1% in the treatment of tinea cruris and tinea corporis. *J Am Acad Dermatol*. 1988; 18(1 Pt 1):52-56.
- ¹²³ Suschka S, Fladung B, Merk HF. Clinical comparison of the efficacy and tolerability of once daily Canesten with twice daily Nizoral (clotrimazole 1% cream vs. ketoconazole 2% cream) during a 28-day topical treatment of interdigital tinea pedis. *Mycoses*. 2002; 45(3-4):91-96.
- ¹²⁴ Evans EG. A comparison of terbinafine (Lamisil) 1% cream given for one week with clotrimazole (Canesten) 1% cream given for four weeks, in the treatment of tinea pedis. *Br J Dermatol*. 1994;130 Suppl 43:12-14.
- ¹²⁵ Schopf R, Hettler O, Brautigam M, et al. Efficacy and tolerability of terbinafine 1% topical solution used for 1 week compared with 4 weeks clotrimazole 1% topical solution in the treatment of interdigital tinea pedis: a randomized, double-blind, multi-centre, 8-week clinical trial. *Mycoses*. 1999; 42(5-6):415-420.
- ¹²⁶ Patel A, Brookman SD, Bullen MU, et al. Topical treatment of interdigital tinea pedis: terbinafine compared with clotrimazole. *Australas J Dermatol*. 1999; 40(4):197-200.
- ¹²⁷ Savin R, Jorizzo J. The safety and efficacy of sertaconazole nitrate cream 2% for tinea pedis. *Cutis*. 2006; 78(4):268-274.
- ¹²⁸ No authors listed. Treatment of tinea versicolor with a new antifungal agent, ciclopirox olamine cream 1%. *Clin Ther*. 1985; 7(5):574-83.
- ¹²⁹ [Tanenbaum L](#), [Anderson C](#), [Rosenberg MJ](#), et al. 1% sulconazole cream v 2% miconazole cream in the treatment of tinea versicolor. A double-blind, multicenter study. *Arch Dermatol*. 1984; 120(2):216-219.
- ¹³⁰ Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. *J Am Acad Dermatol*. 2000; 43(4 Suppl):S70-S80.
- ¹³¹ Elewski BE, Abramovits W, Kempers S, et al. A novel foam formulation of ketoconazole 2% for the treatment of seborrheic dermatitis on multiple body regions. *J Drugs Dermatol*. 2007; 6(10):1001-8.
- ¹³² Elewski B, Ling MR, Phillips TJ. Efficacy and safety of a new once-daily topical ketoconazole 2% gel in the treatment of seborrheic dermatitis: a phase III trial. *J Drugs Dermatol*. 2006; 5(7): 646-50.
- ¹³³ Swinyer LJ, Decroix J, Langner A. Ketoconazole gel 2% in the treatment of moderate to severe seborrheic dermatitis. *Cutis*. 2007; 79(6):475-82.
- ¹³⁴ Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev*. 2007; (3):CD001434.