



Antifungals, Topical

Therapeutic Class Review (TCR)

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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 (Ciclodan™ cream/kit) ⁷	X	X	X	X	X	
ciclopirox (Ciclodan™ solution) ⁸						Topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails due to Trichophyton rubrum
ciclopirox (CNL-8™) ⁹	--	--	--	--	--	
ciclopirox (Pedipirox-4™) ¹⁰						
ciclopirox (Penlac®) ¹¹						
clotrimazole (Desenex®) ¹² (Lotrimin®) ¹³	X	X	X	X	X	--
clotrimazole / betamethasone (Lotrisone®) ¹⁴	X	X	--	X	X	--
econazole ¹⁵	X	X	X	X	X	--
ketoconazole (Extina®) ¹⁶	--	--	--	--	--	Seborrheic dermatitis
ketoconazole cream ¹⁷	X	X	X	X	X	Seborrheic dermatitis
ketoconazole (Ketodan™) ¹⁸			--	--	--	Seborrheic dermatitis
ketoconazole (Nizoral Shampoo®) ¹⁹	--	--	X	--	--	--
ketoconazole (Xolegel®) ²⁰	--	--	--	--	--	Seborrheic dermatitis
miconazole (Azolen™) ²¹	X	--	--	X	--	--
miconazole (Fungoid®) ²²	X	--	--	X	--	--
miconazole (Fungoid-D) ²³	X	--	--	--	--	--
miconazole (Monistat®) ²⁴	X	X	X	X	X	--
miconazole / zinc oxide / white petrolatum (Vusion®) ²⁵	--	--	--	--	--	Diaper dermatitis (adjunctive treatment)

FDA-Approved Indications (continued)

Drug	Tinea pedis	Tinea cruris	Tinea versicolor	Tinea corporis	Cutaneous candidiasis	Other
miconazole (Zeasorb®) ²⁶	X	X	--	--	--	--
naftifine (Naftin®) ²⁷	X	X	--	X	--	--
nystatin ²⁸	--	--	--	--	X	--
nystatin (Pediaderm AF) ²⁹	--	--	--	--	X	--
nystatin / triamcinolone ³⁰	--	--	--	--	X	--
oxiconazole (Oxistat®) ³¹	X	X	X (cream only)	X	--	--
sertaconazole (Ertaczo®) ³²	X	--	--	--	--	--
sulconazole (Exelderm®) ³³	X	X	X	X	--	--
terbinafine (Lamisil®) ³⁴	X	X	X	X	--	--
tolnaftate (Tinactin®) ³⁵	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 (OTC) topical agent.

Drug	Manufacturer
benzoic acid/salicylic acid (Bensal HP)	Seven Oaks
butenafine (Mentax)	Mylan Pharmaceuticals
butenafine OTC	generic
ciclopirox (Ciclodan)	Medimetriks
ciclopirox (CNL-8)	Innocutis Holding
ciclopirox (Loprox)	generic
ciclopirox (Pedipirox-4)	Valeant
ciclopirox (Penlac)	generic
clotrimazole (Desenex) OTC	Novartis
clotrimazole (Lotrimin)	generic
clotrimazole OTC	generic
clotrimazole/betamethasone (Lotrisone)	generic
econazole (Spectazole)	generic
ketoconazole (Extina)	Stiefel
ketoconazole (Ketodan)	Medimetriks
ketoconazole (Nizoral Shampoo)	generic
ketoconazole (Xolegel)	Aqua
ketoconazole cream	generic
miconazole (Azolen) OTC	Stratus
miconazole (Fungoid) OTC	Valeant
miconazole (Fungoid-D) OTC	Valeant
miconazole (Monistat) OTC	generic
miconazole (Nuzole)	Vertical Pharmaceuticals
miconazole (Zeasorb) OTC	Stiefel
miconazole / zinc oxide/ white petrolatum (Vusion)	Stiefel/Physicians
naftifine (Naftin)	Merz
nystatin	generic
nystatin (Pediaderm AF)	Arbor
nystatin/triamcinolone	generic
oxiconazole (Oxistat)	PharmaDerm
sertaconazole (Ertaczo)	Valeant
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*.³⁶ 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.³⁷

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.³⁸

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*.³⁹ 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 pruritus. 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*).⁴⁰ 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 pruritus 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.⁴¹

Seborrheic dermatitis is one of the more common cutaneous diseases.⁴² 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).

PHARMACOLOGY⁴³

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, Desenex), econazole, ketoconazole (Extina, Ketodan, Nizoral Shampoo, Xolegel), miconazole (Azolen, Fungoid, Zeasorb, Monistat, Nuzole, 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.⁴⁴

Ciclopirox (Ciclodan, Pedipirox-4, 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 Pediderm AF) 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^{45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57}

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.⁵⁸ These are topical agents and not intended for ophthalmic, vaginal, or oral use.⁵⁹

Benzoic acid/salicylic acid (Bensal HP) is contraindicated in patients with hypersensitivity type reactions to topical polyethylene glycols.⁶⁰

Ciclopirox (Ciclodan, CNL-8, Loprox, Pedipirox-4, Penlac,) should be avoided in patients with a history of seizure disorders or immunosuppression.^{61,62,63}

Combination products containing corticosteroids 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.^{64,65}

Xolegel contains 34 percent dehydrated alcohol. Extina contains alcohol and propane/butane. So fire, flame, or smoking during and immediately following application of these products should be avoided.^{66,67}

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.⁶⁸

Loprox shampoo has had some rare reports of hair discoloration occurring on patients with light colored hair.⁶⁹

Miconazole (Vusion) should not be used to prevent diaper dermatitis, as in an adult institutional setting. Preventative use may lead to the development of resistance.⁷⁰

DRUG INTERACTIONS⁷¹

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) ⁷²	reported	nr	nr	nr
butenafine (Mentax) ⁷³	<2	<2	<2	<2
ciclopirox (Ciclofan [®] cream/kit) ⁷⁴	reported	reported	reported	nr
ciclopirox (Ciclofan solution), CNL-8, Pedipirox-4, Penlac, ^{75, 76, 77, 78}	1	nr	1	5
ciclopirox (Loprox) ^{79, 80, 81, 82}	7-34	1-5	1-5	nr
clotrimazole (Desenex) ⁸³ (Lotrimin) ⁸⁴	reported	reported	reported	reported
clotrimazole/betamethasone (Lotrisone) ⁸⁵	reported	reported	reported	reported
econazole ⁸⁶	reported	reported	3	reported
ketoconazole (Extina) ⁸⁷	10	≤1	6	≤1
ketoconazole (Ketodan) ⁸⁸	10	≤1	6	≤1
ketoconazole (Nizoral Shampoo) ⁸⁹	nr	<3	<3	nr
ketoconazole (Xolegel) ⁹⁰	4	<1	reported	<1
ketoconazole cream ⁹¹	5	reported	reported	nr
miconazole (Monistat) ⁹²	reported	reported	reported	nr
miconazole (Zeasorb) ⁹³	nr	nr	nr	nr
miconazole cream (Fungoid-D)	nr	nr	nr	nr
miconazole tincture (Azolen, Fungoid) ^{94, 95}	nr	nr	nr	nr
miconazole/zinc oxide/white petrolatum (Vusion) ⁹⁶	reported	reported	reported	reported
naftifine (Naftin) ⁹⁷	5-6	1-2	2	0.5-2
nystatin ⁹⁸	nr	nr	reported	nr
nystatin (Pediaderm AF) ⁹⁹	nr	nr	reported	nr
nystatin/ triamcinolone ¹⁰⁰	reported	reported	reported	nr
oxiconazole (Oxistat) ¹⁰¹	0.7-1.4	0.4-1.6	0.4	0.2
sertaconazole (Ertaczo) ¹⁰²	reported	nr	reported	nr
sulconazole (Exelderm) ¹⁰³	3	3	reported	1
terbinafine (Lamisil) ¹⁰⁴	1-2	1-2	1-2	nr
tolnaftate (Tinactin) ¹⁰⁵	nr	nr	reported	nr

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

The incidence of nail disorders, such as shape change, irritation, ingrown toenail, discoloration, and application site reactions were similar between ciclopirox (Ciclodan, CNL-8, Pediprox-4, Penlac,) and vehicle.

SPECIAL POPULATIONS

Pediatrics

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.¹⁰⁶ 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 of age and older.¹⁰⁷ In addition, butenafine (Mentax), ketoconazole gel (Xolegel), ketoconazole foam (Extina, Ketodan), and sertaconazole (Ertaczo) are approved for use in children ages 12 years and older.¹⁰⁸ 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.¹⁰⁹ 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 (Pediaderm AF) 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.¹¹⁰ Safety and effectiveness of econazole, ketoconazole cream, naftifine (Naftin), sulconazole (Exelderm) and terbinafine (Lamisil) for pediatric patients have not been established.^{111, 112, 113}

Pregnancy¹¹⁴

All agents in this category are Pregnancy Category B with the exception of benzoic acid/salicylic acid (Bensal HP), clotrimazole/betamethasone, econazole, ketoconazole cream, ketoconazole (Extina, Ketodan, Nizoral, Xolegel), miconazole (Azolen, Fungoid, Zeasorb, Monistat, Vusion), 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) ¹¹⁵	Twice daily for seven days	6%/3% ointment	--
butenafine (Mentax) ¹¹⁶	Once to twice daily for one to four weeks	1% cream	Lotrimin Ultra 1% cream
ciclopirox (Loprox) ^{117, 118, 119, 120}	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% gel 0.77% TS suspension 1% shampoo	--
Ciclopirox (Ciclodan) ¹²¹	Cream, kit : twice daily for four weeks	0.77% cream 0.77% cream (co- packaged with skin cleanser combination #23 (Rehyla™) cleanser	--
ciclopirox (Ciclodan) ¹²²	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 (Pedipirox- 4) ¹²³			
ciclopirox (Penlac) ¹²⁴			
ciclopirox (CNL-8) ¹²⁵			
clotrimazole (Desenex) ¹²⁶	Cream: Two to four times daily for up to four weeks	--	AF 1% cream 2% aero powder 2% powder 2% liquid spray
clotrimazole (Azolen) ¹²⁷	Once to twice daily for two to four weeks	--	2% tincture
clotrimazole (Fungoid) ¹²⁸	Once to twice daily for two to four weeks	--	2% tincture/kit
clotrimazole (Lotrimin) ¹²⁹	Two to four times daily for up to four weeks	1% cream 1% solution	AF 1% cream AF 1% solution
clotrimazole / betamethasone (Lotrisone) ¹³⁰	Twice daily for two to four weeks	1% / 0.05% cream 1% / 0.05% lotion	--
econazole ¹³¹	Once to twice daily for two to four weeks	1% cream	--
ketoconazole (Extina) ¹³²	Twice daily for four weeks	2% foam	--
ketoconazole cream ¹³³	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 (Ketodan) ¹³⁴	Twice daily for four weeks	2% foam 2% foam combo package (co-packaged with skin cleanser combination #23 (Rehyla™) cleanser)	--
ketoconazole (Xolegel) ¹³⁵	Daily for two weeks	2% gel	--
ketoconazole (Nizoral Shampoo) ¹³⁶	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% shampoo	A-D 1% shampoo
miconazole (Fungoid-D) ¹³⁷	Apply thin layer once to twice daily (morning and/or night)	--	1% cream
miconazole (Azolen, Fungoid tincture) ¹³⁸	Apply thin layer twice a day (morning and night) on skin, under nails and surrounding cuticle areas.	--	2% tincture
miconazole (Monistat) ^{139,140}	Twice daily for two to four weeks	2% cream	2% powder (Lotrimin AF) 2% liquid (Lotrimin AF) 2% cream 2% spray 2% gel 2% ointment 2% cream (Nuzole)
miconazole (Zeasorb) ¹⁴¹	Twice daily for two to four weeks	--	2% alcohol-gel 2% powder
miconazole / zinc oxide / white petrolatum (Vusion) ¹⁴²	Apply at each diaper change for seven days	0.25% / 15% / 81.35% ointment	--
naftifine (Naftin) ¹⁴³	Cream: daily for four weeks Gel: twice daily for four weeks	1% cream 1% gel	--
nystatin ¹⁴⁴	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 (Pediaderm AF) ¹⁴⁵	Twice daily until healing is complete	Pediaderm AF Complete Kit 100,000 units / gm cream	--

Dosages (continued)

Drug	Frequency of Application	Rx Availability	OTC Availability
nystatin / triamcinolone ¹⁴⁶	Twice daily	100,000 units / gm / 0.1% cream 100,000 units / gm / 0.1% ointment	--
oxiconazole (Oxistat) ¹⁴⁷	Once to twice daily for two to four weeks	1% cream 1% lotion	--
sertaconazole (Ertaczo) ¹⁴⁸	Twice daily for four weeks	2% cream	--
sulconazole (Exelderm) ¹⁴⁹	Once to twice daily for two to four weeks	1% cream 1% solution	--
terbinafine (Lamisil) ¹⁵⁰	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) ¹⁵¹	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.¹⁵² Treatment should continue for at least one week after symptoms have resolved.¹⁵³ 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.¹⁵⁴ 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, respectively) as well as higher mycological cure (61.7 versus 17.6 percent, respectively); however, this difference was not statistically significant at four and eight weeks of treatment.

naftifine (Naftin) versus econazole

Patients with tinea cruris or tinea corporis (n=104) were evaluated in a double-blind, randomized study.¹⁵⁵ 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.¹⁵⁶ 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.¹⁵⁷ 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 were 89.7 percent for terbinafine and 73.1 percent for clotrimazole (p=0.002).

In a double-blind, clinical trial, 429 patients with tinea pedis 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.¹⁵⁸ 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.¹⁵⁹ 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.¹⁶⁰ 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.¹⁶¹ 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.¹⁶² 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.¹⁶³ 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.¹⁶⁴ 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.¹⁶⁵ 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 pruritus 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 316 patients with moderate to severe seborrheic dermatitis.¹⁶⁶ 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

A systematic review was conducted to evaluate topical treatments for fungal infections of the skin and nails of the foot.¹⁶⁷ 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 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 (Ciclodan, CNL-8, Pedipirox-4, Penlac) 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.

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