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
butenafine (Lotrimin Ultra® [OTC])[1]	X	X	--	X	--	Relief of itching, burning, and cracking
butenafine (Mentax®)[2]	X	X	X	X	--	--
ciclopirox 0.77% (Ciclodan® cream/ cream kit)[3,4]	X	X	X	X	X	--
ciclopirox 0.77% (Loprox®/ cream kit/ gel/ suspension kit) [5,6,7,8,9]	X	X	X	X	X	Seborrheic scalp dermatitis (Loprox 1% shampoo only)
ciclopirox 8% (Ciclodan solution; Ciclodan kit, Penlac®)[10,11]	--	--	--	--	--	Topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails due to *Trichophyton rubrum*
clotrimazole (Alevazol [OTC], solution)[12]	--	--	X (RX only)	X	X	For discomfort, scaly skin between the toes or burning feet Relief of itching, burning, and cracking
clotrimazole (Lotrimin® AF cream [OTC])[13]	X	X	--	X	--	Relief of itching, burning, and cracking
clotrimazole / betamethasone (DermacinRx Therazole Pak)[14]	X	X	--	X	--	Caused by the organism *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*
clotrimazole / betamethasone (Lotrisone®, lotion)[15]	X	X	--	X	--	--
econazole cream[16]	X	X	X	X	X	--
econazole foam (Ecoza™)[17]	X	--	--	--	--	--
efinaconazole (Jublia®)[18]	--	--	--	--	--	Topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*
ketoconazole[19]	X	X	X	X	X	Seborrheic dermatitis
ketoconazole (Extina®, Ketodan®)[20], [21]	--	--	--	--	--	Seborrheic dermatitis
ketoconazole (Nizoral® shampoo, Nizoral A-D shampoo)[22]	--	--	X	--	--	--

FDA-Approved Indications (continued)

Drug	Tinea pedis	Tinea cruris	Tinea versicolor	Tinea corporis	Cutaneous candidiasis	Other
ketoconazole (Xolegel®)[23]	--	--	--	--	--	Seborrheic dermatitis
ketoconazole/skin cleanser 28 (Ketodan Foam Kit®)[24]	--	--	--	--	--	Seborrheic dermatitis
luliconazole (Luzu™)[25]	X	X	--	X	--	Caused by the organism *Trichophyton rubrum* and *Epidermophyton floccosum*
miconazole (Desenex [OTC])[26]	X	--	--	--	--	--
miconazole (Azolen™ [OTC])[27]	X	--	--	X	--	--
miconazole (Fungoid®[OTC])[28]	X	--	--	X	--	--
miconazole (Lotrimin AF spray [OTC])[29]	X	X	X	X	X	--
miconazole (Zeasorb AF® [OTC])[30]	X	X	--	--	--	--
miconazole/zinc oxide/ white petrolatum (Vusion®)[31]	--	--	--	--	--	Diaper dermatitis (adjunctive treatment)
naftifine (Naftin®)[32]	X	X	--	X	--	--
nystatin[33]	--	--	--	--	X	--
nystatin/triamcinolone[34]	--	--	--	--	X	--
oxiconazole (Oxistat®)[35]	X	X	X (cream only)	X	--	--
sertaconazole (Ertaczo®)[36]	X	--	--	--	--	--
sulconazole (Exelderm®)[37]	X	X	X	X	--	--
tavaborole (Kerydin™)[38]	--	--	--	--	--	Topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*
terbinafine (Lamisil® [OTC])[39]	X	X	X	X	--	--
terbinafine (Lamisil® AT [OTC])[40]	X	X	-	X	-	--

FDA-Approved Indications (continued)

Drug	Tinea pedis	Tinea cruris	Tinea versicolor	Tinea corporis	Cutaneous candidiasis	Other
tolnaftate (Fungoid-D™ [OTC])[41]	X	--	--	--	--	--
tolnaftate (Tinactin® [OTC])[42]	X	X	X	X	--	--
tolnaftate (Lamisil AF Defense [OTC])[43]	X	--	--	X	--	--
undecylenic acid (Hongo Cura)[44]	X	X	--	X	--	--
undecylenic acid (Sponix Anti-Fungal [OTC])[45]	X	X	--	--	--	--
Undecyclenic acid/ chloroxylenol (Gordochom [OTC])[46]	X	--	--	X	--	Relief of itching, burning, and cracking

Janssen announced the discontinuation of Nizoral 2% shampoo (ketoconazole). The last production will be in October 2018 with an expiry date of September 2020.

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.

Manufacturer Listing

Drug	Manufacturer
butenafine (Mentax)	Mylan
butenafine OTC (Lotrimin Ultra OTC)	generic, Schering-Plough/Bayer
ciclopirox (Ciclodan)	Medimetriks
ciclopirox (Loprox)	generic, Medimetriks/Valeant
ciclopirox (Penlac)	generic, Valeant
clotrimazole OTC (Lotrimin AF)	generic; Schering-Plough/Bayer
clotrimazole OTC (Alevazol)	generic, Capital
clotrimazole/betamethasone (Dermacinrx Therazole Pak)	Puretek
clotrimazole/betamethasone (Lotrisone)	generic; Merck
econazole	generic
econazole (Ecoza)	Exeltis/Glenmark
efinaconazole (Jublia)	Valeant

Manufacturer Listing (continued)

Drug	Manufacturer
ketoconazole	generic
ketoconazole (Extina, Ketodan)	Mylan, Medimetriks
ketoconazole (Nizoral Shampoo, Nizoral A-D Shampoo)	generic; Janssen; Johnson & Johnson Consumer
ketoconazole (Xolegel)	Aqua/Almirall
ketoconazole (Ketodan Kit)	Medimetriks
luliconazole (Luzu)	Oceanside, Valeant
miconazole OTC	generic
miconazole (Azolen) OTC	Stratus
miconazole (Desenex) OTC	GlaxoSmithKline Consumer
miconazole (Fungoid) OTC	Valeant/Pedinol
miconazole (Lotrimin AF) OTC	Schering-Plough/Bayer/MDS Consumer
miconazole (Zeasorb AF) OTC	Crown
miconazole/zinc oxide/white petrolatum (Vusion)	Prestium, Mylan
naftifine	generic
naftifine (Naftin)	Sebela
nystatin	generic
nystatin/triamcinolone	generic
oxiconazole	generic
oxiconazole (Oxistat)	Sandoz
sertaconazole (Ertaczo)	Valeant
sulconazole (Exelderm)	Sun/Journey
tavaborole (Kerydin)[47]	Pharmaderm/Sandoz
terbinafine (Lamisil AT) OTC	generic; Novartis/GSK
tolnaftate (Fungoid-D) OTC	Valeant
tolnaftate (Tinactin) OTC	Schering-Plough/Bayer
tolnaftate (Lamisil AF) OTC	Novartis/GSK
tolnaftate OTC	generic
undecylenic acid (Hongo Cura) solution OTC	Kramer
undecylenic acid (Sponix Anti-Fungal) solution OTC	BioRx
undecyclenic acid/chloroxylenol (Gordochom) solution OTC	Gordon

OVERVIEW

Tinea cruris, corporis, and pedis, named for the body sites involved, are superficial fungal infections (dermatophytosis) caused by 3 genera of dermatophytes: *Trichophyton*, *Microsporum*, and *Epidermophyton.*[48] 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 10% and 20%.[49]

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.[50]

Tinea pedis (athlete's foot) is 1 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*.[51] 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 1 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*).[52] 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% 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.[53] Due to the lack of comparative studies with ciclopirox (Ciclodan, Penlac), efinaconazole (Jublia), and tavaborole (Kerydin) for the treatment of onychomycosis, it is difficult to measure their effectiveness versus other indicated products. An oral antifungal, if tolerated, may lead to higher success rates in the treatment of onychomycosis.[54]

Seborrheic dermatitis is 1 of the more common cutaneous diseases.[55] One proposed etiology is overgrowth of yeast, which normally inhabits sebaceous skin of the scalp, eyebrows, and central face. The disease typically occurs in 3 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).

PHARMACOLOGY[56]

Undecylenic acid (Hongo Cura, Sponix Anti-Fungal) is organic unsaturated fatty acids derived from castor oil that have 11 carbons in the fatty acid chain. The exact mechanism of action of undecylenic acid/undecylenate is unknown. It has been demonstrated that undecylenic acid/undecylenate inhibits morphogenesis of *Candida albicans* by interference with fatty acid biosynthesis, which can inhibit germ tube (hyphae) formation. Medium-chain fatty acids have also been shown to disrupt the pH of the cell cytoplasm by being proton carriers, which interferes with the replication mechanism in infected cells. The mechanism of action and effectiveness in fatty acid based antifungal is dependent on the number of carbon atoms in the chain. The more carbon atoms in a chain, the more effective the fatty acid-based antifungal.

The other agents in this category can be divided into 2 principal pharmacologic antifungal groups, the allylamines and the azoles.

Butenafine (Mentax), a benzylamine, is structurally and pharmacologically related to the allylamine antifungal agents, which include naftifine (Naftin) and terbinafine (Lamisil). 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 (Alevazol, Dermacinrx Therazole Pak, Desenex, Lotrimin AF, Lotrisone), econazole (Ecoza), ketoconazole (Extina, Ketodan, Nizoral Shampoo, Xolegel), miconazole (Azolen, Fungoid, Vusion, Zeasorb AF), 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 to 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.[57]

Efinaconazole (Jublia) is also an azole antifungal. The antifungal activity is attributed to disruption of the normal fungal cell membrane permeability by inhibiting lanosterol 14α-demethylase, which leads to a decrease in ergosterol concentration and accumulation of lanosterol.

Tavaborole (Kerydin) is an oxaborole antifungal with activity attributed to inhibition of fungal protein synthesis. This is done by inhibition of aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS).[58]

Ciclopirox (Ciclodan, Loprox, Penlac) 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 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[59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74]

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[75,76,77,78,79,80,81,82,83,84,85]

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

Ciclopirox (Ciclodan, Loprox, Penlac) should be avoided in patients with a history of seizure disorders or immunosuppression.

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.

Xolegel contains 34% dehydrated alcohol. Extina, Ketodan and Ecoza contain alcohol and propane/butane; therefore, fire, flame, or smoking during and immediately following application of these products should be avoided. Do not store containers in sunlight or expose containers to heat or temperatures above 120^{o}F (49^{o}C), even when empty.

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.

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

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.

Clotrimazole/betamethasone (Lotrisone, Dermacinrx Therazole Pak), undecylenic acid (Hongo Cura; Sponix Anti-Fungal), and undecyclenic acid/chloroxylenol (Gordochom) should not be used to treat or prevent diaper rash.

DRUG INTERACTIONS[86,87,88]

Significant drug interactions with the topical agents have not been noted, with the exception of econazole and luliconazole.

Concomitant administration of warfarin and econazole has resulted in the enhancement of the anticoagulant effect. Monitoring International Normalized Ratio (INR) and/or prothrombin time may be indicated especially for patients who apply econazole to large body surface areas, in the genital area, or under occlusion.

Based on an in vitro assessment, luliconazole has the potential to inhibit cytochrome P-450 (CYP) enzymes 1A2, 2C9, 2C19, 2D6, and 3A4. At therapeutic doses, luliconazole may also inhibit the activity of CYP2C19 and CYP3A4; however, the potential inhibitory activity is theoretical as there have been no *in vivo* drug interaction trials conducted to evaluate the effect of luliconazole on other drugs that are substrates of CYP2C19 and CYP3A4.

ADVERSE EFFECTS[89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115]

Drug	Burning	Itching	Application Site Reaction	Erythema
butenafine (Lotrimin Ultra, Mentax)	< 2	< 2	< 2	< 2
ciclopirox (Ciclodan cream, kit)	reported	reported	reported	nr
ciclopirox (Ciclodan solution, Penlac)	1	nr	1	5
ciclopirox (Loprox cream, kit, suspension)	reported	reported	nr	nr
ciclopirox (Loprox shampoo)	1	1	1	1
clotrimazole (Alevazol, Desenex, Lotrimin AF)	reported	reported	reported	reported
clotrimazole/betamethasone (Dermacinrx Therazole Pak, Lotrisone)	reported	reported	reported	reported
econazole	reported	reported	3	reported
econazole (Ecoza)	nr	nr	< 1	nr
efinaconazole (Jublia)	nr	nr	4.9*	nr

Adverse Effects (continued)

Drug	Burning	Itching	Application Site Reaction	Erythema
ketoconazole	5 (cream) 10 (foam) nr (shampoo)	5 (cream) ≤ 1 (foam) < 3 (shampoo)	5 (cream) 6 (foam) < 3 (shampoo)	nr (cream, shampoo) ≤ 1 (foam)
ketoconazole (Extina)	10	≤ 1	6	≤ 1
ketoconazole (Nizoral Shampoo)	nr	< 3	< 3	nr
ketoconazole (Xolegel)	4	< 1	reported	< 1
luliconazole (Luzu)	nr	nr	< 1	nr
miconazole	reported	reported	reported	nr
miconazole (Zeasorb AF)	nr	nr	nr	nr
miconazole tincture (Azolen, Fungoid)	nr	nr	nr	nr
miconazole/zinc oxide/white petrolatum (Vusion)	reported	reported	reported	reported
naftifine (Naftin 1% gel)	5	1	reported	0.5
naftifine (Naftin 2% cream)	reported	≥ 1	reported	reported
naftifine (Naftin 2% gel)	reported	reported	2%	reported
nystatin	nr	nr	reported	nr
nystatin/triamcinolone	reported	reported	reported	nr
oxiconazole (Oxistat)	0.7-1.4	0.4-1.6	0.4	0.2
sertaconazole (Ertaczo)	reported	nr	reported	nr
sulconazole (Exelderm)	3	3	reported	1
tavaborole (Kerydin)	nr	nr	4	1.6
terbinafine (Lamisil)	1-2	1-2	1-2	nr
tolnaftate cream (Fungoid-D)	nr	nr	nr	nr
tolnaftate (Tinactin)	nr	nr	reported	nr
undecylenic acid (Hongo Cura; Sponix Anti-Fungal)	nr	nr	nr	nr
undecyclenic acid/chloroxylenol (Gordochom)	nr	nr	nr	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

* Application site reactions for efinaconazole were defined as site dermatitis, site vesicles, and site pain.

**Application site reactions for tavaborole were defined as exfoliation and dermatitis.

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

SPECIAL POPULATIONS[116,117,118,119,120,121,122,123,124,125]

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.[126] Drugs which have safety and effectiveness data for children include clotrimazole, miconazole, tolnaftate, and undecylenic acid/chloroxylenol which can be used in patients ages ≥ 2 years; miconazole/zinc oxide/white petrolatum (Vusion) may be used in children ≥ 4 weeks of age. In addition, safety and efficacy of tavaborole (Kerydin) are established in patients ≥ 6 years of age; and butenafine (Mentax), econazole (Ecoza), ketoconazole gel (Xolegel), ketoconazole foam (Extina, Ketodan), and sertaconazole (Ertaczo) are approved for use in children ages ≥ 12 years. 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 < 12 years old. Ciclopirox cream and suspension can be used in patients aged ≥ 10 years, nail lacquer in patients aged ≥ 12 years, and gel and shampoo in patients aged ≥ 16 years. Nystatin can be used at any age, including infancy, while the combination product nystatin/triamcinolone can be used in children ≥ 2 months of age. Clotrimazole/betamethasone is not recommended for those < 17 years of age. Safety and efficacy of luliconazole (Luzu) has been demonstrated in pediatric patients aged ≥ 12 years for tinea pedis and tinea cruris and in those ≥ 2 years old with tinea corporis. Naftifine (Naftin) 2% cream is approved in patients aged ≥ 2 years with tinea corporis and in patients aged ≥ 12 years for interdigital tinea pedis and tinea cruris. Naftifine (Naftin) 2% gel is approved in patients aged ≥ 12 years for interdigital tinea pedis. Safety and effectiveness of econazole, efinaconazole (Jublia), ketoconazole cream, other formulations of naftifine (Naftin), sulconazole (Exelderm), and terbinafine (Lamisil) for pediatric patients have not been established.

Pregnancy

Clotrimazole/betamethasone (DermacinRx Therazole Pak), efinaconazole (Jublia), ketoconazole cream, ketoconazole (Nizoral, Xolegel), miconazole (Azolen, Fungoid, Zeasorb AF), nystatin, nystatin/triamcinolone, sertaconazole (Ertaczo), sulconazole (Exelderm), and tolnaftate are Pregnancy Category C. Previously listed as Pregnancy Category C, the labeling for clotrimazole/betamethasone (Lotrisone), ketoconazole foam (Extina, Ketodan), econazole (Ecoza), luliconazole (Luzu), miconazole/zinc oxide/white petrolatum (Vusion), and tavaborole (Kerydin) have been updated to comply with the Pregnancy Lactation Labeling Rule (PLLR) and now advise that there are no available data for use in pregnant women to inform of a drug-associated risk for major birth defects or miscarriage. Due to the potential for high potency topical corticosteroid use during pregnancy to increase the likelihood for low birthweight infants, clotrimazole/betamethasone should only be used on the smallest area and for the shortest duration, if required during pregnancy.

Undecyclenic acid/chloroxylenol has not been assigned a specific FDA pregnancy risk category rating.

All remaining agents are Pregnancy Category B.

DOSAGES[127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152]

Drug	Frequency of Application	Rx Availability	OTC Availability
butenafine (Lotrimin Ultra OTC)	Tinea pedis: twice daily for 1 week or once daily for 4 weeks Tinea corporis and tinea cruris: once daily for 2 weeks	--	1% cream
butenafine (Mentax)	Tinea pedis: twice daily for 1 week or once daily for 4 weeks Tinea corporis and tinea cruris: once daily for 2 weeks Tinea versicolor: once daily for 2 weeks	1% cream	--
ciclopirox	Cream, gel, topical suspension: twice daily for 4 weeks Shampoo: Apply 5 mL to scalp as directed twice a week for 4 weeks; a minimum of 3 days should occur between applications	0.77% cream, gel, and TS suspension 1% shampoo	--
ciclopirox (Ciclodan)	Cream, kit: twice daily for 4 weeks	0.77% cream; Ciclodan cream kit contains 0.77% ciclopirox cream co-packaged with Rehyla® hair and body cleanser, a cosmetic formula containing chamomile, salicylic acid, and hyaluronic acid	--
ciclopirox (Loprox)	Cream, topical suspension: twice daily for 4 weeks Shampoo: Apply 5 mL to scalp as directed twice a week for 4 weeks; a minimum of 3 days should occur between applications	0.77% cream and TS suspension 1% shampoo Loprox cream kit contains 0.77% ciclopirox cream co-packaged with Rehyla® hair and body cleanser Loprox suspension kit contains ciclopirox 0.77% topical suspension co-packaged with Rehyla hair and body cleanser	--
ciclopirox nail laquer (generic, Ciclodan; Penlac)	Once daily (preferably at bedtime or 8 hours before washing) to all affected nails for 48 weeks; daily applications should be made over the previous coat and removed with alcohol every 7 days	8% nail lacquer topical solution	--

Dosages (continued)

Drug	Frequency of Application	Rx Availability	OTC Availability
clotrimazole	Tinea cruris: twice daily for 2 weeks Tinea corporis and pedis: twice daily for 4 weeks	1% cream; 1% solution	1% cream; 1% solution
clotrimazole (Lotrimin AF)	Tinea cruris: twice daily for 2 weeks Tinea corporis and pedis: twice daily for 4 weeks	--	1% cream
clotrimazole (Alevazol)	Cutaneous candidiasis and tinea cruris: twice daily for 2 weeks Tinea corporis and pedis: twice daily for 4 weeks	--	1% ointment
clotrimazole/ betamethasone	Tinea corporis and cruris: twice daily for 1 to 2 weeks Tinea pedis: twice daily for 2 to 4 weeks	1% / 0.05% cream; 1% / 0.05% lotion	--
clotrimazole/ betamethasone (Dermacinrx Therazole Pak)	Tinea corporis and cruris: twice daily for 1 to 2 weeks Tinea pedis: twice daily for 2 to 4 weeks	1% / 0.05% combo package (co-packaged with Zinc oxide 20% skin healing paste)	--
clotrimazole/ betamethasone (Lotrisone)	Tinea corporis and cruris: twice daily for 1 to 2 weeks Tinea pedis: twice daily for 2 to 4 weeks	1% / 0.05% cream	--
econazole	Tinea cruris, tinea corporis, and tinea versicolor: once daily for 2 weeks Tinea pedis: once daily for 4 weeks Cutaneous candidiasis: twice daily for 2 weeks	1% cream	--
econazole (Ecoza)	Once daily for 4 weeks	1% foam	--
efinaconazole (Jublia)	Apply once daily for 48 weeks to the toenail, toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate using the integrated flow-through brush applicator	10% solution	--
ketoconazole	Cream: once daily for 2 to 6 weeks depending on indication; apply twice daily for 4 weeks or until clinical clearing for seborrheic dermatitis Foam: Twice daily for 4 weeks Shampoo: Twice a week for 4 weeks	2% cream, foam, shampoo	--
ketoconazole (Extina, Ketodan)	Twice daily for 4 weeks	2% foam	--
ketoconazole (Nizoral Shampoo)	Shampoo 2%: use as directed twice a week for 4 weeks Shampoo 1%: use every 3 to 4 days for up to 8 weeks	2% shampoo	A-D 1% shampoo
ketoconazole (Xolegel)	Daily for 2 weeks	2% gel	--

Dosages (continued)

Drug	Frequency of Application	Rx Availability	OTC Availability
luliconazole (Luzu)	Apply a thin layer to the affected area and approximately 1 inch on the immediate surrounding area(s) once daily for 1 week (tinea cruris and corporis) or 2 weeks (tinea pedis)	1% cream	--
miconazole	Twice daily for 2 to 4 weeks	2% cream	2% aerosol powder (Lotrimin AF); 2% cream; 2% ointment; 2% powder (Desenex, Lotrimin AF, Zeasorb AF); 2% liquid spray (Lotrimin AF)
miconazole (Azolen)	Apply thin layer twice a day (morning and night) on skin, under nails, and surrounding cuticle areas for 4 weeks Not effective on scalp or nails	--	2% tincture
miconazole (Fungoid)	Apply thin layer twice a day (morning and night) to affected area for 4 weeks Not effective on scalp or nails	--	2% tincture 2% tincture kit (co-packaged with Nail Scrub lotion)
miconazole/zinc oxide/ white petrolatum (Vusion)	Apply at each diaper change for 7 days	0.25% / 15% / 81.35% ointment	--
naftifine	1% Cream: daily for 4 weeks 2% Cream: once daily for 2 weeks	1% cream; 2% cream	--
naftifine (Naftin)	Cream: once daily for 2 weeks 1% Gel: twice daily for 4 weeks 2% Gel: once daily for 2 weeks	2% cream; 1%, 2% gel	--
nystatin	Cream, ointment: twice daily until healing is complete Powder: 2 to 3 times daily until healing is complete	100,000 units/gm cream; 100,000 units/gm powder; 100,000 units/gm ointment	--
nystatin/triamcinolone	Twice daily	100,000 units/gm / 0.1% cream; 100,000 units/gm / 0.1% ointment	--
oxiconazole	Once to twice daily for 2 to 4 weeks	1% cream	--
oxiconazole (Oxistat)	Once to twice daily for 2 to 4 weeks	1% cream; 1% lotion	--

Dosages (continued)

Drug	Frequency of Application	Rx Availability	OTC Availability
sertaconazole (Ertaczo)	Twice daily for 4 weeks	2% cream	--
sulconazole (Exelderm)	Once to twice daily for 2 to 4 weeks	1% cream; 1% solution	--
tavaborole (Kerydin)	Apply once daily for 48 weeks to entire toenail surface	5% solution	--
terbinafine (Lamisil, Lamisil AT)	Cream: twice daily for 1 to 2 weeks Spray: once or twice daily for 1 week Gel: once daily for 1 week	--	1% cream; 1% spray; 1% gel
tolnaftate	Twice daily for 2 to 4 weeks	--	1% aerosol powder; 1% cream; 1% powder; 1% solution; 1% liquid spray
tolnaftate (Fungoid-D)	Apply thin layer once to twice daily (morning and/or night)	--	1% cream
tolnaftate (Tinactin, Lamisil AF)	Twice daily for 2 to 4 weeks	--	1% aerosol powder; 1% powder; 1% liquid spray (Tinactin only)
undecylenic acid (Hongo Cura)	Tinea cruris: twice daily (morning and night) for 2 weeks Tinea pedis and corporis: twice daily (morning and night) for 4 weeks	--	25% spray
undecylenic acid (Fungi-Nail)	Tinea cruris: twice daily (morning and night) for 2 weeks Tinea pedis and corporis: twice daily (morning and night) for 4 weeks	--	25% solution
undecylenic acid (Sponix Anti-Fungal)	Tinea cruris: twice daily for 2 weeks Tinea pedis: twice daily for 4 weeks	--	22% solution
undecyclenic acid /chloroxylenol (Gordochom)	Tinea corporis: twice daily for 2 weeks Tinea pedis: once daily for 4 weeks	--	25%/3% solution

In general, tinea corporis and tinea cruris require treatment for 2 weeks, whereas tinea pedis may require treatment for up to 4 weeks.[153] Treatment should continue for at least 1 week after symptoms have resolved.[154] Therapy with ciclopirox nail laquer (Ciclodan, Penlac, generic) 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% 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Tinea Cruris and/or Tinea Corporis

butenafine (Mentax) versus clotrimazole

Eighty patients, diagnosed with tinea cruris or tinea corporis, were randomly assigned to butenafine once daily for 2 weeks or clotrimazole twice daily for 4 weeks in a double-blind manner.[155] Follow-up was done at 1, 2, 4, and 8 weeks. At the end of 1 week, butenafine recipients exhibited higher clinical cure rate compared to clotrimazole recipients (26.5 versus 2.9%, respectively), as well as higher mycological cure (61.7 versus 17.6%, respectively); however, this difference was not statistically significant at 4 and 8 weeks of treatment.

luliconazole (Luzu) versus placebo

In a randomized, double-blind, vehicle-controlled, multicenter clinical trial, 256 subjects with a clinical and culture confirmed diagnosis of tinea cruris were evaluated based on the safety and efficacy of luliconazole 1% cream.[156,157] The patients either applied luliconazole 1% cream or vehicle cream to the affected area and approximately 2.5 cm (1 inch) of the surrounding area once daily for 7 days. The signs and symptoms of tinea cruris (erythema, scaling, and pruritus), potassium hydroxide (KOH) examination, and dermatophyte culture were assessed at baseline, end-of-treatment (Day 7), and 2 and 3 weeks post-treatment. The treatment success was defined as complete clearance (clinical cure and mycological cure) at 3 weeks post-treatment. Complete clearance in patients with tinea cruris was demonstrated with luliconazole 1% cream. The 3-week post-treatment outcomes for luliconazole 1% cream (n=165) yielded 21% complete clearance, 43% effective treatment, 24% clinical cure, and 78% mycological cure, as compared to the vehicle cream group (n=91) that yielded 4% complete clearance, 19% effective treatment, 7% clinical cure, and 45% mycological cure.

A multicenter, randomized, double-blind, vehicle-controlled clinical trial established the efficacy of luliconazole for the treatment of tinea corporis in patients ages 2 to < 18 years old (n=75).[158] Patients were randomized to receive either 1% luliconazole cream or vehicle/placebo to the affected area and near surrounding skin once daily for 7 days. Complete clearance (clinical cure and mycological cure) occurred in 71% (80% clinical cure, 80% mycological cure) of those treated with luliconazole versus 36% treated with vehicle (43% clinical cure, 57% mycological cure).

naftifine (Naftin) versus econazole

Patients with tinea cruris or tinea corporis (n=104) were evaluated in a double-blind, randomized study.[159] Naftifine 1% cream or econazole 1% cream were applied to affected areas twice daily for 4 weeks. After 1 week of treatment, naftifine had an overall cure rate of 19% compared with 4% for econazole (p=0.03). Two weeks after the end of treatment, both medications had overall cure rates of approximately 80%. 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% of the econazole subjects.

Sertaconazole (Ertaczo) versus terbinafine (Lamisil) versus luliconazole (Luzu)

Eighty-three patients with tinea corporis and tinea cruris infections were enrolled in this multicenter, randomized, open-label parallel study.[160] The initial treatment phase involved three groups receiving either sertaconazole 2% cream applied topically twice daily for four weeks, terbinafine 1% cream once daily for two weeks, or luliconazole 1% cream once daily for two weeks. At the end of treatment phase, there was a follow-up phase at the end of 2 weeks, where the patients were assessed clinically and mycologically for relapse. Sixty-two enrollees completed the study. The primary efficacy variables, including change in pruritus, erythema, vesicle, desquamation and mycological cure, were significantly improved in all the three groups, as compared to baseline, in the treatment and follow-up phase. A greater proportion of patients in sertaconazole group (85%) showed resolution of pruritus as compared to terbinafine (54.6%) and luliconazole (70%). There was also a greater reduction in mean total composite score (pruritus, erythema, vesicle, and desquamation) in the sertaconazole group (97.1%) as compared to terbinafine (91.2%) and luliconazole (92.9%). All groups showed equal negative mycological assessment without any relapses. All three study drugs were well tolerated. Only one patient in the sertaconazole group withdrew from the study due to suspected allergic contact dermatitis.

Tinea Pedis

econazole foam (Ecoza) versus placebo

In 2 randomized, double-blind, vehicle-controlled, multicenter, clinical trials, 505 patients with interdigital tinea pedis were randomized 1:1 to Ecoza 1% topical foam or vehicle.[161] The patients ranged in age from 12 to 71 years with 5 subjects less than 18 years of age at baseline. Patients applied the assigned medication once daily for 4 weeks. The severity of erythema, scaling, fissuring, maceration, vesiculation, and pruritus were graded using a 4-point scale (none, mild, moderate, severe). Patients had KOH examination and fungal cultures taken to confirm eligibility. A total of 339 subjects with positive fungal cultures were evaluated for efficacy. Efficacy was evaluated on Day 43, 2-weeks post-treatment with treatment success being defined as complete cure (negative KOH and fungal culture and no evidence of clinical disease). Complete cure rates at 2-weeks post treatment (Day 43) were 23.2% for Ecoza 1% topical foam and 2.4% for the foam vehicle in trial 1, and 25.3% for Ecoza 1% topical foam and 4.8% for the foam vehicle in trial 2. The effective treatment (mycological cure and no or mild erythema and/or scaling with all other signs and symptoms absent) and mycological cure (negative KOH and Fungal culture) rates were also measured 2-weeks post-treatment (Day 43). The effective treatment rates for trial 1 were 48.8% for Ecoza 1% foam and 10.8% for the foam vehicle, and trial 2 reflected 48.4% for

Ecoza and 10.8% for the vehicle. The mycological cure rates in trial 1 were 68.3% for Ecoza and 15.7% for the vehicle; in trial 2, the rates were 67% for Ecoza and 18.1% for the vehicle.

ketoconazole (Nizoral) versus clotrimazole

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.[162] Ketoconazole cream was used twice daily, and clotrimazole cream was administered once daily; both were used for 4 weeks. The number of patients with cure or improvement after 4 weeks was comparable (62% clotrimazole group versus 64% ketoconazole group). The mycological response revealed a negative culture and microscopy in 53.1% versus 52.1% of the patients after 14 days, in 76% versus 79.2% after 28 days, and in 83.7% versus 76.9% 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 2 drugs. Better results were obtained under clotrimazole than under ketoconazole for pruritus (97.8% versus 89.6%) and burning/stinging (97.5% versus 89.4%). Treatments appeared comparably safe and tolerable.

luliconazole (Luzu) versus placebo

In 2 randomized, double-blind, vehicle-controlled, multicenter trials, the safety and efficacy of luliconazole 1% cream were evaluated in 423 patients with clinical and culture-confirmed diagnosis of interdigital tinea pedis.[163,164] The randomized patients either applied luliconazole 1% cream or vehicle cream to the entire area of the forefeet, including all interdigital web spaces and approximately 2.5 cm of the surrounding area of the foot, once daily for 14 days. The signs and symptoms of tinea pedis (erythema, scaling, and pruritus), KOH examination, and dermatophyte culture were assessed at baseline, end-of-treatment (Day 14), and 2- and 4-weeks post-treatment. Success was defined as complete clearance (clinical cure and mycological cure) at 4-weeks post-treatment. Complete clearance in patients with interdigital tinea pedis was demonstrated with luliconazole 1% cream. The 4-week post-treatment outcomes for study 1 regarding luliconazole cream (n=106) yielded 26% complete clearance, 48% effective treatment, 29% clinical cure, and 62% mycological cure, as compared to the vehicle cream group (n=103) that yielded 2% complete clearance, 10% effective treatment, 8% clinical cure, and 18% mycological cure. The 4-week post-treatment outcomes for study 2 regarding the luliconazole cream 1% group (n=107) yielded 14% complete clearance, 33% effective treatment, 15% clinical cure, and 56% mycological cure, as compared to the vehicle cream group (n=107) that yielded 3% complete clearance, 15% effective treatment, 4% clinical cure, and 27% mycological cure.

terbinafine (Lamisil) versus clotrimazole

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 1 week (placebo given for the remaining 3 weeks) with the twice daily application of clotrimazole 1% cream for 4 weeks.[165] Mycological cure and effective treatment were assessed 4 and 6 weeks after commencing therapy. Mycological cure rates at 4 weeks were 93.5% for terbinafine and 73.1% for clotrimazole (p=0.0001). Effective treatment rates at 4 weeks were 89.7% for terbinafine and 58.7% for clotrimazole (p=0.0001), and at 6 weeks were 89.7% for terbinafine and 73.1% 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 1 week followed by a vehicle application for 3 weeks, or clotrimazole 1%

solution for 4 weeks.[166] Patients were evaluated at baseline and at weeks 1, 2, 4 (end of treatment), and 8 (end of follow-up). Effective treatment results were similar and were recorded in 83% of terbinafine patients and 82% of clotrimazole patients. Mycological cure and disappearance of signs and symptoms were similar at each assessment visit in the 2 groups. The mycological cure rate was 95% with terbinafine solution and 91% with clotrimazole solution (p=0.05). Mild to moderate adverse events occurred in 4 to 5% 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.[167] Patients received either terbinafine twice daily for 1 week followed by a placebo cream for 5 weeks or clotrimazole twice daily for 4 weeks. Outcome measures were observed at 1, 4, 8, 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% in the terbinafine group were culture-negative after 1 week compared with only 55.8% 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 4 weeks or vehicle control in 2 randomized, double-blind, parallel group, multicenter studies.[168] Results demonstrated a 70.3% mycologic cure reported in the study group versus 36.7% with the vehicle group (p<0.0001). At week 6, 46.7% of the sertaconazole group had successful treatment outcomes versus 14.9% 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.[169] 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 1 and 2, and then post-treatment weeks 1 and 2. Results from the first study demonstrated 49% of the ciclopirox treatment group (n=73) were clinically and mycologically cured after 2 weeks versus 24% of the placebo treatment group (n=72; p<0.001). Results from the second study demonstrated that 77% of the patients treated with ciclopirox cream were clinically and mycologically cured after 2 weeks of treatment versus 45% 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% versus 73%, 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.[170] The medications were applied twice daily for 3 weeks. Of 181 patients analyzed for efficacy at the end of the treatment trial, 93% of the sulconazole patients and 87% of miconazole patients became KOH-negative. The complete clearing of tinea versicolor lesions occurred in 89% of sulconazole-treated patients and 82% of

miconazole-treated patients. Cutaneous adverse effects, predominantly transient itching, were reported in 8 patients receiving sulconazole and in 4 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.[171] 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 1 was 29% for ciclopirox and 11% for the vehicle group. In study 2, mycologic cure rates were 36% and 9%, respectively. The most common adverse reactions were transient and localized to the site of action (e.g., erythema and application site reaction).

efinaconazole (Jublia) versus placebo

In 2 phase 3, multicenter, randomized, double blind clinical studies, the safety and efficacy of efinaconazole 10% solution in the treatment of toenail onychomycosis were evaluated.[172,173] A total of 1,655 subjects were involved in the studies (study 1: n=870, study 2: n=785) with 20% to 50% clinical involvement. The subjects were randomized 3:1 to efinaconazole or vehicle and received once daily applications for 48 weeks, with 4-week post treatment follow-up. Complete cure rate (0% clinical involvement of target toenail, and both negative KOH examination and fungal culture) was the primary endpoint at 52 weeks and debridement was not performed. With efinaconazole, the mycologic cure rates were significantly greater (study 1: 55.2%, study 2: 53.4%) compared with the vehicle ($p<0.001$). The primary endpoint and complete cure was also significantly greater for efinaconazole (study 1: 17.8% versus 3.3%, study 2: 15.2% versus 5.5%, $p<0.001$). In study 1 treatment success for efinaconazole ranged from 21.3% to 44.8% and from 17.9% to 40.2% in study 2, compared with 5.6% to 16.8% and 7% to 15.4%, respectively, with vehicle. Local site reactions (2%) were the adverse events associated with efinaconazole, which were clinically similar to the vehicle.

tavaborole (Kerydin) versus placebo

In 2 multicenter, double-blind, randomized, vehicle-controlled trials, the efficacy and safety of tavaborole 5% solution in the treatment of toenail onychomycosis were evaluated.[174] A total of 1,194 patients were involved in the trial (trial 1: n=593, trial 2: n=601) with 20% to 60% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement. At 52 weeks, following a 48-week treatment period, efficacy assessments were made. The complete cure efficacy endpoint included negative mycology (negative KOH wet mount and negative fungal culture) and completely clear nail (no clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis). The complete cure rate for trial 1 regarding tavaborole 5% solution (n=399) yielded 6.5% complete cure, 15.3% complete or almost complete cure, and 31.1% mycological cure. As compared to the vehicle group (n=194) that yielded 0.5% complete cure, 1.5% complete or almost complete cure, and 7.2% mycological cure. The outcomes for trial 2 regarding the tavaborole 5% solution group (n=396) yielded 9.1% complete cure, 17.9% complete or almost complete cure, and 35.9% mycological cure, as compared to the vehicle group (n=205) that yielded 1.5% complete cure, 3.9% complete or almost complete cure, and 12.2% mycological cure.

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 4 weeks.[175] The primary endpoint was the proportion of subjects achieving an Investigator's Static Global Assessment score of 0 or 1 at week 4 (treatment success). A significantly greater percentage of subjects achieved treatment success using ketoconazole foam than vehicle foam (56% and 42%, respectively; p<0.0001). Ketoconazole foam was well-tolerated with a low incidence of treatment-related adverse events (14%). 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 2 weeks of treatment in moderate to severe seborrheic dermatitis.[176] 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% of patients treated with ketoconazole 2% gel experienced successful treatment in comparison to 13.9% 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.[177] 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 2 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.[178] 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.

A meta-analysis of the efficacy and safety of luliconazole cream 1% in the treatment of dermatophytoses yielded that short-term treatment can result in the complete clearance of dermatophytoses.[179] The luliconazole cream 1% was more effective than controlled drugs or vehicle (week 4: odds ratio [OR], 1.46; 95% confidence interval [CI], 1.12 to 1.91) and no more adverse events occurred in the luliconazole

cream 1% group (week 4: OR, 1.01; 95% CI, 0.71 to 1.44). The analysis strengthens the evidence for luliconazole cream 1% being more effective than vehicle, 1% terbinafine, 1% bifonazole, and 0.1% or 0.5% luliconazole.

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 2 weeks, and tinea pedis may require treatment for 4 weeks. Treatment should continue for at least 1 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.

Data are also lacking for comparative efficacy in the treatment of seborrheic dermatitis. Both ciclopirox (Loprox) and ketoconazole (Extina, Ketodan, 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, Penlac), efinaconazole (Jublia), and tavaborole (Kerydin) for the treatment of onychomycosis, it is difficult to measure their 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 4 weeks and older. The other agents with safety and effectiveness data for children ages 2 years and older are clotrimazole, miconazole, undecylenic acid, undecylenic acid/chloroxylenol, and tolnaftate.

Luliconazole is a newer azole agent that has similar antifungal properties as other available azole products. Luliconazole offers once daily dosing and is dosed for a shorter period of time than other azoles. The duration of therapy is 2 weeks for interdigital tinea pedis and 1 week for tinea corporis and cruris.

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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