Therapeutic Class Overview
Antifungals, Topical

INTRODUCTION

- The topical antifungals are available in multiple dosage forms and are indicated for a number of fungal infections and related conditions. In general, these agents are Food and Drug Administration (FDA)-approved for the treatment of cutaneous candidiasis, onychomycosis, seborrheic dermatitis, tinea corporis, tinea cruris, tinea pedis, and tinea versicolor (*Clinical Pharmacology 2018*).
- The antifungals may be further classified into the following categories based upon their chemical structures: allylamines (naftifine, terbinafine [only available over the counter (OTC)]), azoles (clotrimazole, econazole, efinaconazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, sulconazole), benzylamines (butenafine), hydroxypyridones (ciclopirox), oxaborole (tavaborole), polyenes (nystatin), thiocarbamates (tolnaftate [no FDA-approved formulations]), and miscellaneous (undecylenic acid [no FDA-approved formulations]) (*Micromedex 2018*).
- The topical antifungals are available as single entity and/or combination products. Two combination products, nystatin/triamcinolone and Lotrisone (clotrimazole/betamethasone), contain an antifungal and a corticosteroid preparation. The corticosteroid helps to decrease inflammation and indirectly hasten healing time. The other combination product, Vusion (miconazole/zinc oxide/white petrolatum), contains an antifungal and zinc oxide. Zinc oxide acts as a skin protectant and mild astringent with weak antiseptic properties and helps to promote healing.
- Ciclopirox, clotrimazole, clotrimazole/betamethasone, econazole (cream only), ketoconazole, naftifine (cream only), nystatin, nystatin/triamcinolone, and oxyconazole (cream only) are available generically in several dosage forms.
- Ecoza (econazole nitrate 1% foam) and Luzu (luliconazole) cream were approved in 2013.
- Two molecular entities were approved in 2014 for the topical treatment of adult patients with onychomycosis of the toenails due to select strains of *Trichophyton*, Jublia (efinaconazole 10% topical solution) and Kerydin (tavaborole 5% topical solution). Prior to 2014, ciclopirox 8% solution was the only topical agent available for the treatment of onychomycosis (*Rosen et al 2016*).
- This review focuses primarily on topical antifungal products that are available by prescription. Antifungal products that are used for the treatment of oropharyngeal or vulvovaginal candidiasis are not included. There are several topical antifungal products that are available OTC, and some products are available OTC as well as by prescription. Additionally, some agents within this class have been used safely and effectively for many years; however, there are limited published data evaluating the efficacy of these products for their approved indications.
- Medispan class: Antifungals - Topical.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-entity Products	
clotrimazole	✔ (cream and solution)
Ecoza (econazole)	✔ (cream only)
Ertaczo (sertaconazole)	-
Exelderm (sulconazole)	-
Extina, Nizoral, Xolegel (ketoconazole)	✔ (cream, foam, and shampoo 2%)
Jublia (efinaconazole)	-
Kerydin (tavaborole)	-
Loprox, Penlac (ciclopirox)	✔ (all formulations*)
Luzu (luliconazole)	✔ † (cream)
Mentax (butenafine)	-
Naftin (naftifine)	✔ (cream only)
nystatin	✔ (cream, ointment and powder)
Oxistat (oxiconazole)	✔ (cream only)
Combination Products	
Lotrisone (clotrimazole/betamethasone)	✔ (cream and lotion)
nystatin/triamcinolone	✔ (cream and ointment)
Vusion (miconazole/zinc oxide/white petrolatum)	✔ †

* cream 0.77%, gel 0.77%, shampoo 1%, solution 8%, suspension 0.77%

† Authorized generics for Luzu (luliconazole) cream and Vusion (miconazole/zinc oxide/white petrolatum) ointment are available.

(*Clinical Pharmacology 2018, Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration-Approved Indications for Single-Entity Products

Drug	Tinea corporis	Tinea cruris	Tinea pedis	Tinea versicolor	Seborrheic dermatitis	Cutaneous candidiasis	Onychomycosis
clotrimazole				✔		✔	
econazole (cream)	✔	✔	✔	✔		✔	
Ecoza (econazole) foam			✔ *				
Ertaczo (sertaconazole)			✔ *				
Exelderm (sulconazole)	✔	✔	✔ †	✔			
Extina (ketoconazole)					✔ *		
Jublia (efinaconazole)							✔
Kerydin (tavaborole)							✔ ‡
Loprox (ciclopirox)	✔ §	✔ **	✔ ‡	✔ §	✔ ††	✔ §	
Luzu (luliconazole)	✔	✔	✔				
Mentax (butenafine)				✔			
Naftin‡‡ (naftifine)	✔	✔ *	✔ *				
Nizoral (ketoconazole) cream	✔	✔	✔	✔	✔	✔	
Nizoral (ketoconazole) shampoo				✔ §§			
Nystatin						✔	
Oxistat (oxiconazole) ***	✔	✔	✔	✔ †††			
Penlac (ciclopirox lotion)							✔ ‡‡‡
Xolegel (ketoconazole) gel					✔ *		

* Indicated for ≥ 12 years
† The cream is indicated for all tinea infections, but the solution is not indicated for tinea pedis
‡ Safety and efficacy have been established in patients ≥ 6 years of age.
§ Cream, gel, and lotion
** Cream and lotion
†† Gel and shampoo
‡‡ 2% gel only indicated for tinea pedis in patients ≥ 12 years of age. 2% cream may be used for tinea corporis in patients ≥ 2 years of age.
§§ Shampoo 2%
*** The cream is approved for pediatric patients for all indications
††† Cream only
‡‡‡ Indicated as a component of a comprehensive management program, as topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement.

Table 3. Food and Drug Administration-Approved Indications for Combination Products

Drug	Tinea corporis	Tinea cruris	Tinea pedis	Diaper dermatitis	Cutaneous candidiasis
Lotrisone* (clotrimazole/betamethasone)	✔	✔	✔		
nystatin/triamcinolone					✔
Vusion (miconazole/zinc oxide/white petrolatum)				✔ †	

* Indicated for >17 years for inflammatory conditions

† For the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast), in immunocompetent pediatric patients 4 weeks and older

(*Prescribing information: ciclopirox gel 2017, ciclopirox lotion 2014, ciclopirox olamine cream 2017, ciclopirox shampoo 2017, ciclopirox solution 2017, clotrimazole cream 2014, clotrimazole solution 2012, clotrimazole/betamethasone 2018, econazole 2018, Ecoza 2016, Ertaczo 2017, Exelderm cream 2018, Exelderm solution 2018, Extina 2018, Jublia 2016, Kerydin 2018, ketoconazole 2016, Lotrisone 2018, Luzu 2018, Mentax 2018, Naftin 1% gel 2018, Naftin 2% cream 2018, Naftin 2% gel 2018, Nizoral 2017, Nizoral A-D 2015, nystatin cream 2017, nystatin ointment 2017, nystatin powder 2017, nystatin/triamcinolone cream 2017, nystatin/triamcinolone ointment 2016, Oxistat 2016, Vusion 2013, Xolegel 2012*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Several clinical trials have demonstrated that topical azoles (clotrimazole, miconazole, sulconazole), ciclopirox, and nystatin were effective in the management of cutaneous candidiasis (*Bagatell et al 1985, Beveridge et al 1977, Rajan et al 1983, Tanenbaum et al 1983*). Clinical studies have reported no significant difference in efficacy between sulconazole cream and clotrimazole or miconazole cream for cutaneous candidiasis. Nystatin/triamcinolone was compared to the administration of nystatin monotherapy (*Beveridge et al 1977*). The results of this study demonstrated that nystatin/triamcinolone was as effective as nystatin monotherapy. Also, there was no difference reported in the patient or physician preference for either agent.
- There are limited data evaluating the efficacy of the combination of miconazole/zinc oxide for the treatment of patients with diaper dermatitis complicated by candidiasis. In 2 clinical trials, this combination product was compared to patients receiving zinc oxide monotherapy. In 1 study, miconazole/zinc oxide demonstrated statistically significant reductions in total rash scores in patients with mild-to-moderate diaper dermatitis as compared to zinc oxide monotherapy (*Concannon et al 2001*). A second study determined that miconazole/zinc oxide had a lower incidence of diaper dermatitis and a higher clinical microbiological and overall cure rate as compared to patients treated with zinc oxide alone (*Spraker et al 2006*).
- Topical antifungal agents are the mainstay of treatment for seborrheic dermatitis. During clinical trials, ciclopirox gel and shampoo formulations demonstrated statistically significant improvements in symptom scores and clinical cure compared to placebo vehicles (*Aly et al 2003[a], 2003[b], Vardy et al 2000*). Ketoconazole cream, foam, gel, and shampoo formulations were also associated with statistically significant improvements in symptom scores and clinical cure compared to placebo vehicles (*Carr et al 1987, Cauwenbergh et al 1986, Elewski et al 2006, Elewski et al 2007, Green et al 1987)*. There are limited data comparing ciclopirox to ketoconazole. One study reported significantly higher rates of remission with ciclopirox cream (twice daily for 28 days then once daily for 28 days) than ketoconazole gel (twice weekly for 28 days then once weekly for 28 days) for the treatment of facial seborrheic dermatitis (*Naldi and Rebora 2009*). The results were difficult to interpret because ciclopirox was dosed more frequently than ketoconazole. In a recent systematic review, ciclopirox and ketoconazole were both strongly recommended for facial seborrheic dermatitis due to their consistent effectiveness across multiple high-quality trials (*Gupta and Versteeg 2017*).
- Noninvasive tinea fungal infections may be treated with appropriate skin care and a topical antifungal agent (*Andrews et al 2008, Brown and Dresser 2017, Drake et al 1996[a]*). Based on data obtained from clinical trials on tinea pedis, there was a statistically significant improvement in efficacy (microbiological and clinical cure) in patients treated with the following agents compared to placebo: butenafine, ciclopirox, econazole foam, luliconazole, naftifine, oxiconazole, sertaconazole, and tolnaftate (*Aly et al 1989, Aly et al 2003, Ecoza prescribing information, 2013, Gupta et al 2005, Jarratt et al 2013, Jones et al 2014, Pariser et al 1994, Reyes et al 1997, Stein Gold et al 2013, Tschen et al 1997*). In a

meta-analysis of placebo-controlled trials, the pooled relative risks of failure to cure skin infections of the foot were as follows for the topical antifungal agents: allylamines 0.33, azoles 0.3, butenafine 0.33, ciclopirox 0.27, and tolnaftate 0.19 (*Crawford et al 2007*). No differences were detected between individual azoles and allylamines. Meta-analysis of data collected in 9 trials comparing 4 to 6 weeks of treatment with allylamines and azoles showed a risk ratio for treatment failure of 0.63 in favor of allylamines. In another meta-analysis, allylamines, azoles and other antifungals were found to be more effective in mycological cure and sustained cure vs. placebo (*Rotta et al 2012*). No differences were found between the classes of agents.

- Based on data obtained from clinical trials on various tinea infections (which included patients with tinea pedis, corporis, cruris, and/or versicolor), there was a statistically significant improvement in efficacy (microbiological and clinical cure) in patients treated with the following agents compared to placebo: miconazole, naftifine, oxiconazole, and terbinafine (*Jordan et al 1990, Kagawa et al 1989, Mandy and Garrott 1974, Pariser et al 1994, Ramelet et al 1987*). In a meta-analysis of 27 trials, terbinafine demonstrated 70 to 90% and 70 to 80% efficacy in the treatment of dermatomycoses and tinea versicolor, respectively (*Villars et al 1989*). Most of the head-to-head trials comparing one antifungal to another were conducted in a small number of patients. In general, direct comparative trials did not demonstrate that one antifungal was safer or more efficacious than another.
- The combination product consisting of clotrimazole/betamethasone has been evaluated for the treatment of tinea infections. In 2 double-blind, placebo-controlled trials, patients were randomized to clotrimazole/betamethasone, clotrimazole monotherapy, or betamethasone monotherapy. One trial enrolled patients with only a confirmed diagnosis of tinea cruris (*Wortzel et al 1982*). This study showed that 80, 20, and 13% of patients achieved either complete cure or excellent response to therapy with the combination product, clotrimazole monotherapy, and betamethasone monotherapy, respectively. The other study enrolled patients with a confirmed diagnosis of moderate-to-severe tinea cruris or tinea corporis (*Katz et al 1984*). This study showed that for the treatment of tinea cruris and tinea corporis, patients treated with the combination product had significantly better total sign and symptom reductions compared to each individual component administered as monotherapy.
- A Cochrane review of 129 trials (N = 18,086) assessed the effects of topical antifungal treatments in tinea cruris and tinea corporis (*El Gohary et al 2014*). Mycological cure rates favored naftifine 1% compared to placebo in 3 studies (risk ratio [RR] 2.38, 95% confidence interval [CI] 1.80 to 3.14, number needed to treat [NNT] 3, 95% CI 2 to 4) (low quality evidence). In 1 study, naftifine 1% was more effective than placebo in achieving clinical cure (RR 2.42, 95% CI 1.41 to 4.16, NNT 3, 95% CI 2 to 5) (low quality evidence). Across 2 studies, mycological cure rates were superior for clotrimazole 1% compared to placebo (RR 2.87, 95% CI 2.28 to 3.62, NNT 2, 95% CI 2 to 3). There was no difference in mycological cure between azoles and benzylamines (RR 1.01, 95% CI 0.94 to 1.07) (low quality evidence). There was no evidence for a difference in cure rates between tinea cruris and tinea corporis.
- Ciclopirox solution (lacquer) is a topical antifungal that is FDA-approved for onychomycosis. Two double-blind, placebo-controlled clinical trials reported significantly higher mycologic cure rates for ciclopirox (29 to 36%) compared to vehicle (9 to 11%) (*Katz et al 1984*). Both studies reported significantly higher treatment successes (≤ 10% nail involvement and negative mycology) with ciclopirox (6.5 to 12%) than placebo (0.9%). One of the 2 studies reported a significantly higher treatment cure (clear nail and negative mycology) with ciclopirox (5.5 to 8.5%) vs placebo (0 to 0.9%). A meta-analysis of randomized trials concluded that there was some evidence that ciclopirox was effective for the management of onychomycosis, but ciclopirox had to be applied daily for prolonged periods (1 year) (*Crawford et al 2007*). Oral antifungals are generally recommended for the treatment of onychomycosis (*de Berker 2009, Drake et al 1996[c], Ameen et al 2014*). Topical antifungals should be considered for patients who have contraindications to systemic therapy. There is inconsistent evidence that combining topical and oral antifungals leads to better cure rates than monotherapy with oral antifungals.
- The safety and efficacy of Jublia applied once daily for the treatment of onychomycosis of the toenail were assessed in 2 identical, 52-week prospective, multi-center, randomized, double-blind, vehicle-controlled clinical trials in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement. The primary endpoint was complete cure rate defined as 0% clinical involvement of target toenail (no clinical evidence of onychomycosis) in addition to mycologic cure (defined as both negative potassium hydroxide [KOH] examination and fungal culture) at week 52. Complete cure was significantly greater for patients treated with Jublia compared to vehicle in both studies (17.8% in study 1 and 15.2% in study 2 compared with 3.3% and 5.5% for vehicle, respectively; $p < 0.001$ for both studies). Similarly, mycologic cure rates were also significantly greater for patients treated with Jublia compared to vehicle in both studies (55.2% in study 1 and

53.4% in study 2 compared with 16.8% and 16.9% for vehicle, respectively; p < 0.001 for both studies). Similar adverse events were reported between the 2 groups (*Elewski et al 2013, Valeant Pharmaceuticals press release 2014*).

- The safety and efficacy of Kerydin were demonstrated in two phase 3, randomized, parallel-group, double-blind, vehicle-controlled trials: Study 301 and 302. Both studies were identically designed and patients (N = 1194) had 20 to 60% of clinical involvement of the target toenail at baseline. Patients were randomized to receive either Kerydin 5% topical solution or a vehicle-control which was applied topically once daily for 48 weeks. The primary endpoint, which was complete cure (defined as 0% clinical involvement of the target nail plus a negative KOH and fungal culture) was observed in 6.5% of Kerydin-treated patients vs 0.5% in the vehicle-controlled group for Study 301, and 9.1% vs 1.5%, respectively, in Study 302 (p ≤ 0.001 for both studies). Mycologic cure (defined as a negative KOH wet mount and a negative fungal culture) was observed in 31.1% of Kerydin-treated patients vs. 7.2% in the vehicle-controlled group for Study 301, and 35.9% vs 12.2%, respectively, in Study 302 (p ≤ 0.001 for both studies). The most common treatment-related adverse events in the Kerydin and vehicle-control groups were application site exfoliation (2.7% and 0.3%, respectively), erythema (1.6% and 0%), and dermatitis (1.3% and 0%) (*Elewski et al 2015*). In a pooled analysis of patients with complete or almost clear nails who completed an additional 8 weeks of post-study follow-up (N = 62), complete cure was maintained in 28.6% of Keridyn-treated patients compared to 7.7% of the vehicle-controlled group (*Gupta et al 2018*).
- In a 2014 evidence-based review of topical therapy for toenail onychomycosis, 28 studies evaluating complete and mycological cure demonstrated that topical amorolfine (not available in the US), ciclopirox, tavaborole, and efinaconazole were effective for patients with less than 50 to 65% toenail involvement. A treatment duration of 48 weeks led to the most successful outcomes. Complete cure (generally defined as mycological cure with no nail involvement) rates were 17.8% with efinaconazole vs 8.5% with ciclopirox (*Gupta et al 2014b*).

Table 4. Results from Phase 3 Trials of FDA-Approved Topical Treatments for Onychomycosis
This table provides an indirect comparison of data collected from different clinical trials. Because study populations and trial methods may vary across trials, this information should not be used to draw conclusions about the relative efficacy or safety of individual treatments.*†

Antifungal	Dosing and Duration	Complete or Clinical Cure	Mycologic Cure
Jublia (efinaconazole) Baseline: 20 to 50% clinical involvement	Once daily applications for 48 weeks of treatment with a 4 week follow-up period	15.2 to 17.8% Difference from vehicle-control, 9.7 to 14.5%	53.5 to 55.2% Difference from vehicle-control, 36.5 to 38.4%
Kerydin (tavaborole) Baseline: 20 to 60% clinical involvement	Once daily applications for 48 weeks of treatment with a 4 week follow-up period	6.5 to 9.1% Difference from vehicle-control, 6 to 7.6%	31.1 to 35.9% Difference from vehicle-control, 23.8%
Penlac (ciclopirox) nail lacquer Baseline: 20 to 65% clinical involvement	Applied for 48 weeks	5.5 to 8.5% Difference from vehicle-control, 4.6 to 8.5%	29 to 36% Difference from vehicle-control, 18 to 27%

*Only first-to-market topical drug formulations are included for comparison.
†According to the Penlac prescribing information, concomitant use of ciclopirox 8% topical solution and systemic antifungal agents for onychomycosis is not recommended because studies have not been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents. Some experts support the recommendation of combination therapy; however, this has not been explicitly studied by the manufacturer or evaluated by the FDA.

(*Poulakos et al 2017, Rosen et al 2016, Westerberg et al 2013*)

CLINICAL GUIDELINES

- National and international recommendations which discuss the management of fungal infections focus primarily on superficial mycotic infections. Several recommendations list topical antifungal agents or subclasses, and generally do

not give preference to one agent vs another (*Brown and Dresser 2017, de Berker 2009, Drake et al 1996[a], Drake et al 1996[b], Naldi and Rebora 2009, Ameen et al 2014, Stevens et al 2014*). According to these guidelines, mycological and clinical cure of noninvasive fungal infections are often achieved with topical therapy alone. Oral therapy is preferred for the treatment of extensive or severe infection and those with tinea capitis or onychomycosis.

- New topical antifungal agents Jublia (efinaconazole) and Kerydin (tavaborole) are recommended for mild-moderate toenail fungal infections (*Brown and Dresser 2017*).

SAFETY SUMMARY

- If patients experience hypersensitivity to an agent, therapy should be discontinued. Cross-sensitivity can also occur among the imidazole-containing agents.
- Products containing corticosteroids should be used with caution because systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticoid insufficiency after withdrawal of treatment. Conditions which augment systemic absorption include use over large surface areas, prolonged use, use under occlusive dressings, and use in pediatric patients.
- The use of topical corticosteroids (ie, betamethasone) may increase the risk of posterior subcapsular cataracts and glaucoma.
- The most common adverse events are erythema, stinging, blistering, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.
- Several products are flammable: Ecoza (econazole), Extina (ketoconazole), Penlac (ciclopirox), Xolegel (ketoconazole), Jublia (efinconazole), and Kerydin (tavaborole). They should not be used near heat or flame.
- Econazole may potentiate the effects of warfarin and increase bleeding risk. Luliconazole may inhibit cytochrome P450 (CYP) 2C19.

DOSING AND ADMINISTRATION

- For all products: enough cream/ointment/lotion should be applied to cover the affected areas and the immediately surrounding skin. If a patient shows no clinical improvement after the treatment period, the diagnosis and therapy should be reviewed.

Table 5. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Single-entity products			
clotrimazole	Topical cream, solution	Apply twice daily for up to 4 weeks.	External use only; not for ophthalmic use.
econazole (Ecoza and generics)	Topical cream: (generics) Topical foam: (Ecoza)	**Cream** *Candidiasis:* Apply twice daily for 2 weeks. *Other uses:* Apply once daily for 2 weeks; except pedis, for 4 weeks. **Foam** *Tinea pedis:* Apply once daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Ertaczo (sertaconazole)	Topical cream	Apply twice daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Exelderm (sulconazole)	Topical cream Topical solution	**Cream** *Corporis, cruris, versicolor:* Apply once or twice daily for 3 weeks. *Pedis*: Apply twice daily for 4 weeks. **Solution** *Corporis, cruris, versicolor*: Apply once or twice daily for 3 weeks	Topical use only; not for ophthalmic use.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Extina, Nizoral, Xolegel (ketoconazole)	Topical cream, foam, shampoo, gel	**Cream** *Dermatitis*: Apply twice daily for 4 weeks or until clinical clearing. *Other uses*: Apply once daily for 2 weeks; except for tinea pedis for 6 weeks. **Foam**: Apply twice daily for 4 weeks. **Shampoo 2%:** Apply to damp skin of the affected area. Lather, leave in place for 5 minutes, and then rinse off with water. One application of the shampoo should be sufficient. **Shampoo 1% (OTC):** Apply to wet hair. Generously lather, rinse, and repeat. Use every 3 to 4 days for up to 8 weeks. **Topical Gel:** Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Jublia (efinaconazole)	Topical solution	Apply to affected toenails once daily for 48 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use. Ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.
Kerydin (tavaborole)	Topical solution	Apply to the affected toenails once daily for 48 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use. Should be applied to the entire toenail surface and under the tip of each toenail being treated.
Loprox, Penlac (ciclopirox)	Topical cream, gel, lotion, shampoo, solution	**Cream and lotion**: Apply twice daily for up to 4 weeks. **Gel**: Apply twice daily for 4 weeks. **Shampoo:** Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications. **Solution**: Apply once daily (preferably at bedtime or 8 hours before washing) to all affected nails, evenly over the entire nail plate. Do not remove on a daily basis. Daily applications should be made over the previous coat and removed with alcohol every 7 days.	Solution: Should be applied to the nail bed, hyponychium, and under the surface of the nail plate when it is free of the nail bed. Topical use only; not for oral, ophthalmic, or intravaginal use
Luzu (luliconazole)	Topical cream	**Interdigital tinea pedis:** Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Tinea cruris or tinea corporis: Apply once daily for 1 week.	
Mentax (butenafine)	Topical cream	Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use
Naftin (naftifine)	Topical cream, gel	**Cream/Gel 2%:** Apply once daily for 2 weeks. **Gel 1%**: Apply twice daily for up to 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use
nystatin	Topical cream, ointment, powder	**Cream and ointment**: Apply twice daily until complete healing. **Powder**: Apply 2 to 3 times daily until complete healing.	Topical use only; not for oral, ophthalmic, or intravaginal use Cream is usually preferred to ointment in candidiasis involving intertriginous areas. Very moist lesions are best treated with topical powder.
Oxistat (oxiconazole)	Topical cream, lotion	**Corporis and cruris**: Apply once or twice daily for 2 weeks. **Versicolor**: Apply once daily for 2 weeks. **Pedis**: Apply once or twice daily for one month.	Shake lotion well before using. Topical use only; not for oral, ophthalmic, or intravaginal use
Combination products			
Lotrisone (clotrimazole/ betamethasone)	Topical cream, lotion	**Corporis, cruris**: Apply twice daily for up to 2 weeks. **Pedis**: Apply twice daily for up to 4 weeks.	Do not use more than 45 grams or 45 mL per week. Shake lotion well before each use. Topical use only; not for oral, ophthalmic, or intravaginal use
nystatin/ triamcinolone	Topical cream, ointment: nystatin 100,000 units/ triamcinolone 1 mg/gram	Apply twice daily for up to 25 days.	For external use only; not for ophthalmic use
Vusion (miconazole/zinc oxide/white petrolatum)	Topical ointment: 0.25% miconazole nitrate/15% zinc oxide/81.35% white petrolatum	Apply with each diaper change for 7 days.	Topical use only; not for oral, ophthalmic, or intravaginal use

See the current prescribing information for full details.

CONCLUSION

- Many of the products are available generically, including ciclopirox, clotrimazole, clotrimazole/betamethasone, econazole cream, ketoconazole, naftifine cream, nystatin, nystatin/triamcinolone, and oxyconazole cream.
- Several topical antifungal products are available OTC and some are available both as prescription and OTC.
- The limited clinical trials available do not differentiate one product from another in terms of mycological and clinical cure.

- Vusion (miconazole/zinc oxide/white petrolatum) is a combination product indicated for diaper dermatitis when complicated by documented candidiasis. It has been shown to be more effective than zinc oxide therapy alone (*Concannon et al 2001, Spraker et al 2006*). Comparative trials to other active agents have not been conducted.
- Jublia is the first FDA-approved triazole antifungal indicated for the topical treatment of adult patients with onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.* Jublia is also the first triazole antifungal to be developed for the treatment of distal lateral subungual onychomycosis (DLSO) (*Valeant Pharmaceuticals press release 2014*).
- Kerydin is a first-in-class oxaborole topical antifungal approved for the treatment of toenail onychomycosis (*MarketWatch press release 2014*). Jublia is also approved for this indication.
- National and international recommendations which discuss the management of fungal infections focus primarily on superficial mycotic infections. Several recommendations list topical antifungal agents or subclasses, and generally do not give preference to one agent vs another (*Brown and Dresser 2017, de Berker, 2009, Drake et al 1996[a], Drake et al 1996[b], Naldi and Rebora 2009, Ameen et al 2014, Stevens et al 2014*). According to these guidelines, mycological and clinical cure of noninvasive fungal infections are often achieved with topical therapy alone.
- Dosing and administration of these agents are dependent upon the condition being treated and the patient population.
- Adverse effects for the topical antifungals are primarily dermatological with allergic or contact dermatitis, burning, dry skin, erythema, pruritus, skin irritation, and stinging as the most common reactions reported.

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