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Abbreviated Class Update: Topical Antifungal Agents

Month/Year of Review: September 2014
End date of literature search: July 2014
PDL Class: Dermatologic – Topical antifungal
New drugs: efinaconazole (JUBLIA®)
tavaborole (KERYDIN®)

Date of Last Review: March 2014
Source Document: OSU College of Pharmacy

Manufacturer: Valeant Pharmaceuticals
Anacor Pharmaceuticals

Current PDL Status: Only miconazole cream, nystatin cream and nystatin ointment are preferred (Appendix 1).

Background: The Oregon Health Plan list of prioritized services does not fund treatment for CANDIDIASIS OF MOUTH, SKIN AND NAILS or DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS in immune-competent hosts. Topical antifungal agents are solely indicated for these and other related non-funded conditions (Appendix 1).

Prior Authorization (PA) criteria: Required for non-preferred agents covering only for a funded diagnosis and trial of generic formulation (Appendix 2).

Research Questions:
- Is there any new evidence for differences in efficacy or safety in topical antifungal drugs that would indicate changes are needed to the current PDL?
- Is efinaconazole or tavaborole more effective and/or safer than currently available agents?
- Are there subgroups of patients where efinaconazole or tavaborole may be more effective or safer than currently available agents?

Conclusions
- There was no new evidence supporting a difference in efficacy/effectiveness or harms between topical antifungals.
- There is moderate level evidence from two placebo-controlled trials that daily application of efinaconazole 10% solution cures onychomycosis in immune competent patients better than the vehicle alone (study 1: 17.8% vs 3.3%, study 2: 15.2% vs 5.5%, P <0.001) and there were no serious adverse events reported.
- There were no published trials identified evaluating tavaborole.

Recommendations:
- Evaluate comparative costs in executive session.

Previous Conclusions and Recommendations

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- There is low quality evidence based on one published fair quality study that luliconazole is effective and safe for the treatment of tinea cruris and is significantly better than placebo in achieving a complete response (21.2% vs. 4.4%; p<0.001).[1] There are no comparative data between luliconazole and other topical antifungal agents. Maintain luliconazole a non-preferred topical antifungal medication on the PDL due to lack of long term clinical outcomes data and direct comparative data to suggest better tolerability or efficacy than currently available agents.

Reason for Review:

Efinaconazole 10% solution (JUBLIA®)[2] and tavaborole 5% solution (KERYDIN®)[3] were approved by the FDA for the for treatment of onychomycosis of the toenails caused by the organisms *Trichophyton rubrum* and *Trichophyton mentagrophytes* since the last review of this class in March 2014. This update will examine their place in therapy and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Methods:

A Medline (Ovid) literature search was conducted for new systematic reviews, meta-analyses, randomized controlled trials (RCT's) and controlled clinical trials comparing antifungal agents head-to-head in the treatment of topical fungal infections and limits for humans, English language with the following search terms: antifungal agents, efinaconazole, tavaborol, tinea, tinea unguium, tinea capitis, tinea corporis, tinea cruis, tinea pedis, pityriasis verscicolor, Candidiasis, Onychomycosis. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Clinical Evidence published a review (October 2013)[4] of treatments for toe onychomycosis which included: topical amorolfine, butenafine, ciclopirox, fluconazole, ketoconazole, terbinafine, tioconazole as well as oral itrconazole, terbinafine and fluconazole. While evidence supported increased cure rates for oral itraconazole and terbinafine, there was no evidence found for topical agents except ciclopirox which modestly improved symptoms over placebo.

New Guidelines:

No new or updated guidelines were identified.

New Safety Alerts, Indications:

No new safety alerts or indications were found.

New Drug Evaluation: efinaconazole 10% solution
FDA approved indications: Topical treatment of onychomycosis of the toenails caused by the organisms *Trichophyton rubrum and Trichophyton mentagrophytes*.

Potential Off-label Use: Other fungal infections of the skin or nails.

Clinical Efficacy Data: Efficacy was established in two (study 1: N = 870, study 2: N = 785) good quality multi-center, double-blinded, randomized vehicle controlled trials.[5] Patients were immune-competent adults with 20-50% fungal involvement of a great toe without dermatophytomas or lunula involvement with positive culture of dermatophyte with or without Candida less than or equal to 42 days before baseline. Patients were randomized (3:1) to efinaconazole or vehicle, once daily for 48 weeks, with a 4-week follow-up. The primary outcome was complete cure at 52 weeks and was greater for efinaconazole (study 1: 17.8% vs 3.3%, study 2: 15.2% vs 5.5%, P <0.001).

Clinical Safety: Application site dermatitis was the most common adverse reaction leading to discontinuation. The rate of discontinuations for adverse events was low overall (efinaconazole vs vehicle: study 1: 3.2% vs 0.5%, study 2: 1.9% vs 0%).[5] Other adverse events reported did not significantly differ between efinaconazole and the vehicle.

New Drug Evaluation: tavaborole 5% solution

FDA approved indications: Topical treatment of onychomycosis of the toenails caused by the organisms *Trichophyton rubrum and Trichophyton mentagrophytes*.

Potential Off-label Use: Other fungal infections of the skin or nails.

Clinical Efficacy Data: No published trials were identified.

Clinical Safety:

References:

1. Jones TM, Jarratt MT, Mendez-Moguel I, et al. A Randomized, Multicenter, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Luliconazole Cream 1% Once Daily for 7 Days in Patients Aged [greater than or equal to] 12 Years With Tinea Cruris. *Journal of Drugs in Dermatology*. 2014;13(1):32+.

2. Label - Jublia. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203567s000lbl.pdf. Accessed August 5, 2014.

3. LABEL - Kerydin. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204427s000lbl.pdf. Accessed August 5, 2014.

4. Ferrari J. Fungal toenail infections. In: *Clinical Evidence*. [on-line database].; 2013. Available at: http://clinicalevidence.bmj.com.liboff.ohsu.edu/x/pdf/clinical-evidence/en-gb/systematic-review/1715.pdf. Accessed August 5, 2014.

5. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. *Journal of the American Academy of Dermatology*. 2013;68(4):600-608. doi:10.1016/j.jaad.2012.10.013.

Appendix 1 – PDL Status and FDA Indications

Generic	Brand	Form	Tinea versicolor	tinea pedis	tinea corporis	tinea cruris	onycho-mycosis	seborrheic dermatitis of the scalp	cutaneous candidiasis
Preferred									
MICONAZOLE NITRATE	MICATIN	CREAM (G)		X	X	X			
NYSTATIN	NYSTATIN	CREAM (G)							X
NYSTATIN	NYSTATIN	OINT. (G)							X
Non-Preferred									
BUTENAFINE HCL	LOTRIMIN ULTRA	CREAM (G)	X	X	X	X			
BUTENAFINE HCL	MENTAX	CREAM (G)	X	X	X	X			
CICLOPIROX	CICLODAN, PENLAC	SOLUTION		X	X				
CICLOPIROX	CICLOPIROX	GEL (GRAM)		X	X				
CICLOPIROX	LOPROX	SHAMPOO						X	
CICLOPIROX/NAIL LACQ/FT DEOD#4	PEDIPIROX-4	KIT					X		
CICLOPIROX/NAIL LACQUER REMOVR	CNL 8	KIT					X		
CLOTRIMAZOLE	LOTRIMIN AF, DESENEX	CREAM (G)	X			X			X
CLOTRIMAZOLE	CLOTRIMAZOLE	SOLUTION	X						X
ECONAZOLE NITRATE	ECOZA	CREAM (G)	X	X	X	X			X
KETOCONAZOLE	KETOCONAZOLE	CREAM (G)	X	X	X	X		X	X
KETOCONAZOLE	NIZORAL	SHAMPOO	X					X	
KETOCONAZOLE	XOLEGEL	GEL (GRAM)						X	
KETOCONAZOLE	EXTINA	FOAM						X	
KETOCONAZOLE	KETODAN	FOAM						X	
LULICONAZOLE	LUZU	CREAM (G)		X	X	X			
MICONAZOLE NITRATE	DESENEX; LOTRIMIN AF	AERO POWD		X	X	X			
MICONAZOLE NITRATE	DESENEX; LOTRIMIN AF	POWDER		X	X	X			
MICONAZOLE NITRATE	FUNGOID TINCTURE	TINCTURE		X	X	X			
MICONAZOLE NITRATE	FUNGOID TINCTURE	KIT		X	X	X			
MICONAZOLE NITRATE	MICATIN	OINT. (G)		X	X	X			
MICONAZOLE NITRATE	DESENEX; LOTRIMIN AF	SPRAY		X	X	X			
NAFTIFINE HCL	NAFTIN	CREAM (G)		X	X	X			
NAFTIFINE HCL	NAFTIN	GEL (GRAM)		X	X	X			

NYSTATIN	NYSTATIN	POWDER							X
NYSTATIN/EMOLLIENT COMBO NO.54	PEDIADERM AF	CREAM (G)							X
NYSTATIN/TRIAMCIN	NYSTATIN-TRIAMCINOLONE	CREAM (G)							
NYSTATIN/TRIAMCIN	NYSTATIN-TRIAMCINOLONE	OINT. (G)							
OXICONAZOLE NITRATE	OXISTAT	CREAM (G)	X	X	X	X			
OXICONAZOLE NITRATE	OXISTAT	LOTION	X	X	X	X			
SERTACONAZOLE NITRATE	ERTACZO	CREAM (G)		X					
SULCONAZOLE NITRATE	EXELDERM	CREAM (G)		X	X	X			
SULCONAZOLE NITRATE	EXELDERM	SOLUTION		X	X	X			
TERBINAFINE HCL	LAMISIL AT	CREAM (G)		X	X	X			
TERBINAFINE HCL	LAMISIL AT	GEL (GRAM)		X	X	X			
TERBINAFINE HCL	LAMISIL	SPRAY		X	X	X			
TOLNAFTATE	TINACTIN	AERO POWD		X	X	X			
TOLNAFTATE	TINACTIN	CREAM (G)		X	X	X			
TOLNAFTATE	(various)	SOLUTION		X	X	X			
TOLNAFTATE	TINACTIN	SPRAY		X	X	X			
UNDECYLENIC ACID	ANTI-FUNGAL	SOLUTION		X		X			

Appendix 2

Antifungals

Goal(s):

- Approve use of antifungals only for ~~covered~~ funded diagnoses. Minor fungal infections of skin, such as dermatophytosis of nail and skin are only covered when complicated by an immunocompromised host.

Length of Authorization:

See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Table 1 – Examples of FUNDED~~COVERED~~ indications (~~41~~/1/~~1406~~)

ICD-9	Description
112.1	Candidiasis of vulva and vagina
112.2	Candidiasis of other urogenital sites
112.4	Candidiasis of the lung
112.5	Disseminated Candidiasis
112.81	Candidal Endocarditis
112.82-112.89	Candidal Otitis Externa - Other Candidiasis site
114.0-114.9	Coccidiomycosis various sites
115.00-115.99	Histoplamosis
116.0-116.2	Blastomycosis
117 & subsets	Rhinosporidosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
118	Mycosis, Opportinistic
518.6	Bronchopulmonary Aspergillus, Allergic
616 & subsets	Inflammatory disease of cervix vagina and vulva
681 & subsets	Cellulitis and abscess of finger and toe
771.7	Neonatal Candida infection

Table 2 – Examples of NON-~~COVERED~~ FUNDED indications (~~41~~/1/14~~06~~)

ICD-9	Description
110.1	Dermatophytosis of nail (onychomycosis)
111.0	Pityriasis versicolor
111.2	Tinea blanca
111.3	Black piedra
111.8	Dermatomycoses nec
111.9	Dermatomycosis nos
112.3	Cutaneous candidiasis
112.9	Candidiasis site nos
690 & subsets	Erythematosquamous dermatosis
691	Atopic dermatitis and related conditions
691.0	Diaper or napkin rash
691.8	Other atopic dermatitis and related conditions
692 & subsets	Contact dermatitis and other eczema
695.2-695.4	Erythema nodosum, rosacea, lupus erythematosus
695.8-695.9	Other specified erythematous conditions, erythematous cond nec, unspecified erythematous condition
697 & subsets	Lichen
706 & subsets	Diseases of sebaceous glands
782.1	Nonspecif skin erupt nec

Table 3 – Criteria driven diagnoses (~~41~~/1/14~~06~~)

ICD-9	Description
~~110.~~	~~Dermatophytosis~~
110.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
~~110.1~~	~~Dermatophytosis of nail (onychomycosis)~~
110.2	Dermatophytosis of hand (tinea manuum)
110.3	Dermatophytosis of groin and perianal area (tinea cruris)
110.4	Dermatophytosis of foot (tinea pedis)
110.5	Dermatophytosis of body (tinea corporis / tinea imbricate)

110.6	Deep seated dermatophytosis
110.8	Dermatophytosis of other specified sites
110.9	Dermatophytosis site of unspecified site
111.1	Tinea nigra
112.0	Candidosis of mouth

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis? See Table 1, Examples of ~~COVERED~~ FUNDED indications (4/1/14~~1/1/06~~)?	Yes: Go to #3.	No: Go to #4.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy & Therapeutics Committee~~Health Resources Commission (HRC).~~	Yes: Inform provider of covered alternatives in class.	No: Approve for 3 months or course of treatment.
4. Is the diagnosis in Table 2? See Examples of NOT-FUNDED~~COVERED~~ indications (4/1/14~~1/1/06~~)	Yes: Pass to RPH: Deny, (Not Covered by the OHP).	No: Got to #5.
5. Is the diagnosis in Table 3, Criteria driven diagnoses (4/1/14~~1/1/06~~)?	Yes: Go to #6.	No: Go to #8.

Approval Criteria		
6. Is the client immunocompromised? • Does the client have a current (not history of) diagnosis of cancer **AND** is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. **OR** • Does the client have a diagnosis of HIV/AIDS? **OR** • Does client have diagnosis of diabetes that requires anti-diabetic medications e.g. Insulin, metformin, glyburide, or any drug in the therapeutic class of Diabetic Therapy? Document medication(s). **OR** • Does client have sickle cell anemia?	Yes: Record ICD-9 code. Approve as follows: (Immunocompromised client) **ORAL** • Toenails = 12 weeks. Max 1 course per year. • Fingernails = 6 weeks. Max 1 course every 6 months. **ORAL & TOPICAL** • All other diagnosis = course of treatment only with PRN renewals. • If length of therapy is unknown, approve for 3 months.	No: Go to #7.

Approval Criteria		
7. Is client currently taking an immunosuppressive drug? Document drug. **Pass to RPH for evaluation if drug not in list.** Immunosuppressive drugs include but are not limited to: **Generic** / **Brand** azathioprine — Imuran basiliximab — Simulect cyclosporine — Sandimmune, Neoral sirolimus — Rapamune tacrolimus — Prograf methotrexate (Mtx) — Rheumatrex hydroxychloriquin — Plaquenil etanercept — Enbrel leflunomide — Arava	Yes: Approve as follows: (Immunocompromised client) **ORAL** • Toenails = 12 weeks. Max 1 course per year. • Fingernails = 6 weeks. Max 1 course every 6 months. **ORAL & TOPICAL** • All other diagnosis = course of treatment only with PRN renewals. • If length of therapy is unknown, approve for 3 months.	No: Pass to RPH; Deny, (Not Covered by the OHP)

Approval Criteria

8. RPH only: All other indications need to be evaluated to see if they are above or below the line diagnosis:

    - If above the line fungal code, then it may be approved for treatment course with prn renewals. If length of therapy is unknown, approve for 3 months intervals only.

    - If below the line: Deny, (Not Covered by the OHP).
        - Deny Non-fungal diagnosis (Medical Appropriateness)
        - Deny Fungal ICD-9 codes that do not appear on the OHP list pending a more specific diagnosis code (Not Covered by the OHP).
        - Forward any fungal ICD-9 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.

P&T / DUR Action: *09/23/2014 (KK); 03/27/2014 (BL); 09/16/10 (KS/DO); 2/23/06; 11/10/0; 9/15/05; 5/12/05*
Revision(s): *1/1/11; 7/1/06; 11/1/0; 9/1/0*
Initiated:

Appendix 3: Specific Drug Information

EFINACONAZOLE 10% SOLUTION[2]

CLINICAL PHARMACOLOGY

Efinaconazole is an azole antifungal. It inhibits fungal lanosterol 14 alpha-demethylase which is necessary for the biosynthesis of ergosterol, a component of fungal cell membranes.

PHARMACOKINETICS

Systemic absorption was studied in 18 adults with onychomycosis. After 28 days of daily application the Cmax was 0.67 ng/mL. In a separate study of healthy volunteers, the plasma half-life was determined to be 29.9 hours.

DOSE & AVAILABILITY

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10%	solution	topical	daily x 48 weeks with the integrated flow-through brush applicator	NA	NA	The safety and effectiveness in pediatric patients have not been established.	No dose adjustment is necessary for the elderly.	Ensure the toe nail, the toe nail folds, toe nail bed, hyponychium, and the undersurface of the toe nail plate, are completely covered.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for Efinaconazole at this time.

Warnings and Precautions: None.

Pregnancy Category: C.

Adverse Reactions: application site vessicles, ingrown toenail, application site pain, and application site dermatitis were the most common adverse reactions occurring $\geq$ 1%.

TAVABOROLE 5% SOLUTION[3]

CLINICAL PHARMACOLOGY

Tavaborole is an oxaborole antifungal gal. It inhibits fungal protein synthesis.

PHARMACOKINETICS

Systemic absorption was studied in 24 adults with onychomycosis. After 2 weeks of daily topicl dosing, the mean Cmax was 5.17 ± 3.47 ng/mL.

DOSE & AVAILABILITY

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5%	solution	topical	daily x 48 weeks with the integrated flow-through brush applicator	NA	NA	The safety and effectiveness in pediatric patients have not been established.	No dose adjustment is necessary for the elderly.	Should be applied to the en tire toenail surface and under the tip of each toenail being treated

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for tavaborole at this time.

Warnings and Precautions: None.

Pregnancy Category: C.

Adverse Reactions: application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis were the most common adverse reactions occurring ≥ 1%.