

Month/Year of Review: March 2013

PDL Classes: Topical Antifungals

Date of Last Review: February 2010

Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: NYSTATIN CREAM/OINTMENT, MICONAZOLE CREAM
- Non Preferred Agents: TOLNAFTATE, KETOCONAZOLE, CLOTRIMAZOLE, CICLOPIROX, ECONAZOLE, NAFTIFINE, BUTENAFINE, SULCONAZOLE, OXICONAZOLE (OXISTAT),

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events

PA Criteria/QL:

- PA required for non-preferred agents covering only for a covered diagnosis and trial of a generic formulation (Appendix 1).

Methods:

A Medline OVID search was conducted with the following search terms: clotrimazole, tolnaftate, naftifine, econazole, butenafine, ciclopirox, sulconazole, sertaconazole, miconazole, nystatin, terbinafine, oxiconazole, tinea unguium, tinea capitis, tinea corporis, tinea cruris, tinea pedis, lichen planus, pityriasis versicolor, Candidiasis, vulvovaginal candida, Blastomycosis, Coccidioidomycosis, Cryptococcosis, mycosis, Histoplasmosis, Onychomycosis, tinea, Chromoblastomycosis, seborrheic dermatitis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to December week 3 2012.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

New Trials:

A total of 210 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or non-antifungal), or outcome (non-clinical). After review of titles and abstracts for inclusion, four relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Two trials compared oral fluconazole and a topical antifungal agent to treat vaginal yeast infections. Consolaro et al¹ showed fluconazole was more effective at eradicating vaginal candidiasis than topical nystatin (87% to 74%; p<0.05). A trial Sekhavat et al² also demonstrated fluconazole as superior to intra-vaginal clotrimazole (80.5% vs. 70%; p<0.001). Both trials were fair to low quality; blinding was an issue for both trials, neither trial discussed treatment allocation, and randomization methods were not clearly explained.

A low quality study by Dehghan et al³ compared topical clotrimazole with oral fluconazole for treating adults with tinea versicolor. At the end of twelve weeks both groups had high rates of response (92% clotrimazole vs. 81.8% fluconazole, p=0.77) but the difference between the two treatments was not significant.

A low quality small study by Chen et al⁴ looked at the adjunctive efficacy of using topical treatment in children with tinea capitis. Patients were randomized to use either 1% selenium sulfide or 1% ciclopirox shampoo with oral griseofulvin for eight weeks. At the end of treatment 91.7% of children using selenium sulfide and 90.4% of children using ciclopirox had a mycological cure; the difference between the shampoos was not statistically significant.

New drugs:

No new topical antifungal medications were approved.

New Formulations/Indications:

A new buccal formulation of miconazole was approved in April 2010. Oravig™ is indicated for the treatment of oropharyngeal candidiasis for patients over 16 years old.⁵

New FDA safety alerts:

No new safety alerts were found for topical antifungals.

New Systematic Reviews:

No new or updated, relevant systematic reviews were identified. A protocol for a future systematic review⁶ was published at the Cochrane Collaboration. This review will try to establish any efficacy differences in topical antifungals for tinea cruris and corporis. No date was given for estimated completion.

Guidelines:

The updated sexually transmitted disease guideline⁷ from the Centers for Disease Control was reviewed. No changes regarding the use of antifungals were found.

Recommendations:

- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

1. Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermatologica Venereologica*. 2012;92(1):78–82.
2. Sekhavat L, Tabatabaie A, Tezerjani FZ. Oral fluconazole 150mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *Journal of Infection and Public Health*. 2011;4(4):195–199.
3. Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010;37(8):699–702.
4. Chen C, Koch LH, Dice JE, et al. A Randomized, Double-Blind Study Comparing the Efficacy of Selenium Sulfide Shampoo 1% and Ciclopirox Shampoo 1% as Adjunctive Treatments for Tinea Capitis in Children. *Pediatric Dermatology*. 2010;27(5):459–462.
5. Oravig prescribing information. *Strativa Pharmaceuticals, Woodcliff Lake NJ*. 2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022404lbl.pdf. Accessed December 17, 2012.
6. El-Gohary M, Burgess H, Doney L, et al. Topical antifungal treatments for tinea cruris and tinea corporis. In: The Cochrane Collaboration, El-Gohary M, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: <http://doi.wiley.com/10.1002/14651858.CD009992>. Accessed January 9, 2013.
7. Workowski KA. Sexually Transmitted Diseases Treatment Guidelines, 2010. *CDC.gov*. 2010. Available at: <http://www.cdc.gov/MMWR/preview/mmwrhtml/rr5912a1.htm>. Accessed December 28, 2012.

Appendix 1

Randomized Control Trials

Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermatologica Venereologica*. 2012; 92(1):78–82.

The aim of this study was to determine and compare the efficacy of treatment with fluconazole and nystatin in Brazilian women with vaginal Candida. In a population of 932 women, vaginal cultures were performed for yeasts, whether or not the women showed signs and symptoms of vulvovaginal candidiasis. Yeasts were isolated from 12.2% of the women (114/932): 53.2% of the yeasts were *Candida albicans*, 27.0% *C. glabrata*, 13.5% *C. tropicalis* and 6.3% *C. parapsilosis*. Treatment was carried out with both drugs. The overall mean cure rates with fluconazole (87.0%) and nystatin (74.0%) were similar; among women with non-*albicans*, the cure rate with fluconazole was 100%, whereas that with nystatin was 44.4%. The cure rate for women with *C. albicans* was high with both fluconazole and nystatin; however, for those with non-*albicans* species the cure rate was excellent with fluconazole and very low with nystatin, differing from the majority of in vitro studies.

Sekhvat L, Tabatabaie A, Tezerjani FZ. Oral fluconazole 150mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *Journal of Infection and Public Health*. 2011; 4(4):195–199.

To compare the safety and efficacy of fluconazole 150 mg single dose and intra-vaginal clotrimazole 200mg per day for six days in the treatment of the acute episode of vulvovaginal candidiasis (VVC). **METHODS:** In a prospective study, 142 patients with acute clinical and mycological confirmed VVC were enrolled and divided randomly in two groups. 70 patients received intra-vaginal tablet (200mg) daily for seven days, whereas 72 patients received single dose oral fluconazole (150 mg). Second and third visits were done for all patients seven days and one month after treatment and the clinical and mycological outcomes evaluated. The analysis performed using SPSS statistical software (version 15). **RESULTS:** At the second visit, 61 patients (84.7%) were cured clinically (inflammation and discharge) and 58 patients (80.5%) mycologically in fluconazole group and 60 patients (83.3%) were cured clinically and 49 patients (70%) mycologically in clotrimazole group ($P=0.01$). At the third visit, only one patient in fluconazole group and 17 patients in clotrimazole group had clinical sign of VVC ($P=0.001$). **CONCLUSION:** Oral fluconazole single dose seems to be a valid and promising therapy to cure acute signs and symptoms of VVC.

Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010; 37(8):699–702.

This study was designed to compare the therapeutic effects of topical clotrimazole and systemic fluconazole in pityriasis versicolor. A double-blind randomized controlled trial was carried out in the dermatological clinic of Gorgan, northern Iran, between April 2006 and May 2007. All consecutive patients with pityriasis versicolor were included and randomly divided into two groups. In the first group (G1), patients underwent treatment with a single dose of fluconazole capsule (400 mg) and placebo cream. In the second group (G2), patients underwent treatment with clotrimazole cream (twice daily) and placebo capsule. The course of treatment was 2 weeks. All subjects were re-evaluated 2, 4 and 12 weeks after the end of the therapeutic course. After 2 weeks, the rate of complete resolution of disease was significantly higher in G2 than G1 (49.1% vs 30%). After 4 weeks, 41 patients (81.2%) of G1 and 52 patients (94.9%) of G2 showed complete resolution. After 12 weeks, 46 patients (92%) in G1 and 45 patients (81.8%) in G2 showed complete resolution. Recurrence rate in G1 and G2 were 6% and 18.2%, respectively. No complications were seen in either group. In this study, clinical response at week 4 was greater in the clotrimazole group than the fluconazole group. Recurrence at week 12 after treatment was less with oral fluconazole than clotrimazole cream. So, for better evaluation, more studies need to be done.

Chen C, Koch LH, Dice JE, et al. A Randomized, Double-Blind Study Comparing the Efficacy of Selenium Sulfide Shampoo 1% and Ciclopirox Shampoo 1% as Adjunctive Treatments for Tinea Capitis in Children. *Pediatric Dermatology*. 2010; 27(5):459–462.

Our objective was to compare the efficacy of selenium sulfide shampoo 1% and ciclopirox shampoo 1% as adjunctive treatments for tinea capitis in children. Forty children aged 1–11 years with clinically diagnosed tinea capitis were randomized to receive selenium sulfide shampoo 1% or ciclopirox shampoo 1% twice a week as adjuncts to an 8-week course of ultramicronized griseofulvin dosed at 10–12 mg/kg/day. At weeks 2, 4, and 8, subjects returned to the clinic for evaluation and scalp cultures. Subjects then returned for follow-up visits 4 weeks after completing treatment. Overall, by 8 weeks, 30 of 33 (90.9%) treated children demonstrated mycological cure. Selenium sulfide shampoo 1% and ciclopirox shampoo 1% were equally effective as adjunctive treatments for tinea capitis in children in our study.