

Topical Antifungal Drugs for Onychomycosis

Executive Summary

- Diagnosis of onychomycosis is based on patient history, clinical exam, microscopy, and culture.
- Treatment of onychomycosis can be frustrating for patients and providers due to high failure and recurrence rates.
- While topical treatments will be the focus of this review, oral agents have been proven to be more effective.
- No matter the therapeutic option chosen, the affected toenail can require 12 to 18 months to grow out, further frustrating patients.
- The efficacy endpoints in studies leading to FDA approval include mycological cure rate, and a combined mycological and clinical cure rate. The agents are typically compared to vehicle products.
- Direct comparisons between recent entrants, efinaconazole (Jublia) and tavaborole (Kerydin), and the older topical agent, ciclopirox (Penlac), are limited by the lack of head-to-head studies, differences in study design, study size, population demographics, degree of nail involvement, definition of “cure,” follow-up time frame, and side effect profile assessments.
- There are variations in bottle design and application procedures of the topical agents that might affect choice amongst the agents.
- Newer agents address the fungal etiology of the disease. In spite of this mechanism of action, the best complete cure rate leaves more than 80% of patients uncured as defined by the FDA. For comparison, some of the oral agents, such as terbinafine (Lamisil), have success rates exceeding 50%, are well tolerated, do not have application issues, and now cost significantly less.

Background

- There has been no previous onychomycosis subclass review. All products in this subclass review are currently formulary on the Uniform Formulary.
- The P&T Committee recommended prior authorization criteria for efinaconazole and tavaborole in February 2015 due to the modest efficacy of the products, lack of head-to-head clinical trials, limited efficacy and safety data, and high cost.
- Epidemiologic studies suggest an onychomycosis prevalence rate of 2% to 14%, more commonly in adults. Genetics, environment, and Tinea are thought to be causative factors and can also contribute to high recurrence rates. *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Epidermophyton floccosum* are commonly identified as sources.
- Poor prognosis for the condition includes more than 50% nail involvement, dermatophytoma or matrix involvement, and immunosuppression. Diagnosis is solidified with use of potassium hydroxide or fungal culture.
- Military Health System expenditures for topical antifungals significantly increased after the approval of the more recent entrants, efinaconazole and tavaborole. Ciclopirox was the first in the class to obtain approval in late 1990s and is now available in generic form. It was the sole prescription topical agent until the recent entrants became available. Poor cure rates limited ciclopirox utilization and continue to hinder broader use of recent entrants.
- The agents are all indicated for use in onychomycosis. Study designs focus on patients with limited to moderate nail involvement that require 48 weeks of treatment and may be limited by application issues. All agents can be combined in practice with debridement, but that approach is part of the ciclopirox label. Alternative options include oral agents, laser therapy, and topical resins.
- See Table 1 for the drugs in the subclass.

Table 1: Drugs in the Class

Topical Antifungal Onychomycosis Subclass			
Generic	ciclopirox	tavaborole	efinaconazole
Brand	Penlac	Kerydin	Jublia
Manufacturer	Valeant Bermuda	Anacor	Valeant
Approval Year	1999	2014	
Dose/Frequency	Apply daily		
Indication	Topical treatment of toenail onychomycosis due to dermatophytes <i>Trichophyton rubrum</i> +/- <i>Trichophyton mentagrophytes</i>		

- While oral agents are not part of this subclass review. However, their efficacy and safety data will be used for comparison purposes, noting the limits of diverse study populations, study designs, and limitations due to the lack of head-to-head studies.
- Issues with the oral agents include concerns regarding drug-drug interactions, rare liver toxicity issues, and the potential need for lab monitoring. Terbinafine (Lamisil) and itraconazole (Sporanox, Onmel) have FDA indications for treatment of onychomycosis in immunocompetent patients. While fluconazole (Diflucan) does not have an FDA indication for onychomycosis, it does have efficacy data to support off-label use.
- Therapies not reviewed but used in treatment of onychomycosis: laser therapy, topical cosmetic resins, debridement

Summary of the Evidence

Efficacy:

- Available meta-analyses do not include all recent entrants in their comparison of available therapies and are limited in their inclusion of mixed disease states. Rotta (*JAMA* 2013) revealed that terbinafine had statistical superiority when compared to other topical therapies such as ciclopirox, while Gupta (*J Am Podr* 2015) suggests topical treatments have equivalent efficacy when comparing mycological cure. Gupta also finds oral terbinafine to be superior to all topical treatments.
- There have been no head-to-head trials comparing the recent entrants. The studies completed to date use a vehicle agent as the control arm of the study. FDA standards include a primary endpoint at one year of complete cure for onychomycosis trials. This encompasses a mycological component, with negative fungal culture and potassium hydroxide, as well as a subjectively “clear” toenail. The trials examining the recent entrants approach one year in length, but have limited follow-up data beyond that period; this limits ability to assess recurrence among the patients studied.
- Study P3-01 and P3-02 examined efinaconazole efficacy and safety in over 1,600 patients and were pivotal trials for FDA approval. While 1,236 patients were in the active arm, the remaining received a vehicle placebo. The complete cure rates were 17.8% and 15.2% for the active arms versus 3.3% and 5.5% in the vehicle arms in the two trials, respectively.
- Study 301 and 302 examined tavaborole efficacy and safety in nearly 1,200 patients and were pivotal trials for FDA approval. While 796 were in the active arm, the remaining received vehicle placebo. The complete cure rates were 6.5% and 9.1% for the active arms versus 0.5% and 1.5% in the vehicles in the two trials, respectively.
- Among alternative topical agents, ciclopirox has efficacy data to support complete cure rates of 5.5% to 8.5%. Maximum nail involvement studied differed among the agents, with the ciclopirox patients having as much as 65% nail involvement, while the tavaborole had 60%, and efinaconazole had 50%. Effectiveness by degree of involvement is not available in the published literature.
- For comparison, terbinafine administered orally was able to achieve 38% complete cure in the FDA pivotal trial leading to approval, and efficacy studies done since FDA approval have achieved complete cures in excess of 50%.
- Relapse rates are not delineated at this time for the newer agents. Ciclopirox has a reported 40% three-month relapse rate, while terbinafine has five-year relapse rate of 20%.

Safety:

- In regards to safety, adverse events were similar to the vehicle-only groups in both trials. Safety issues are rare overall and the safety profile for the topical agents are similar. The adverse event rates centered on application site reactions, including exfoliation, ingrown toenail, dermatitis, vesicles, and site pain. Aside from hypersensitivity issues and limiting treatment to topical use as directed, there are no significant drug-drug interactions and no warnings or precautions for the newer topical agents.

Other Factors:

- There are differences among dispensers for the newer agents, which may result in wastage. While tavaborole uses a simple dropper method, efinaconazole uses a brush applicator method. Ciclopirox is lacquer-based and requires removal after each continuous week of application and, unlike the newer agents, creates a tacky effect after application. The newer agents do have significant percentages of alcohol as an ingredient and require a flammability warning.
- Overall, oral agents, especially terbinafine, provide the gold standard treatment option when treating onychomycosis. While providers and patients have historically had concerns about tolerability of the oral agents, the risks are probably overestimated in practice. While the newer agents provide additional alternative topical treatments for onychomycosis, there continues to be a need for significant improvement in success rates of topical treatments for those few patients that are unable to tolerate oral agents.

References

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