Efinaconazole 10% Solution
A New Topical Treatment for Onychomycosis:
Contact Sensitization and Skin Irritation Potential

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ABSTRACT
Background: Onychomycosis is a chronic condition that often requires long-term management to eradicate the causative fungus, allow a healthy nail to grow, and prevent relapse. As a successful outcome depends highly on patient adherence with treatment, a low risk of periungual skin irritation with topical medication is clinically relevant. Objectives: To study the potential for efinaconazole 10% solution and its corresponding vehicle to induce delayed contact skin sensitization and evaluate its skin irritation potential. Methods: Efinaconazole 10% solution and its vehicle were studied in 239 healthy volunteers for the potential to induce contact skin sensitization. This included a series of induction, challenge, and re-challenge phases. An additional 21-day cumulative irritation study was undertaken in 35 healthy volunteers to compare three concentrations of efinaconazole (1%, 5%, and 10%), vehicle, and positive/negative controls. Results: There was no evidence of induced contact sensitization under occlusive, semi-occlusive, and open (open rub-in) applications of efinaconazole 10% solution. Efinaconazole 1%, 5%, and 10% solutions have mean cumulative irritancy indices of 1.12, 1.26, and 1.18, respectively, where a range of >0 to ≤1 is classified as “mildly irritating.” Results were comparable to vehicle (1.04). Conclusion: Efinaconazole 10% solution did not cause contact sensitization and induced only minimal skin irritation in the studies completed. (J Clin Aesthet Dermatol. 2013;6(3):20–24.)

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lacquer is the only topical agent approved by the United States Food and Drug Administration (FDA) in the United States, despite a relatively low cure rate. With nail application, the most common adverse event with ciclopirox is mild erythema, noted in five percent of the treated population. In an unpublished, 21-day, cumulative, irritant study with ciclopirox, mild transient erythema was seen in 46 percent of subjects, 32 percent with vehicle and two percent with the negative control. Although not a commonly encountered problem, a few cases of allergic contact dermatitis have been reported with topical therapies for onychomycosis. Three cases were associated with amorolfine nail lacquer or cream (not available in the United States) and few cases have also been reported with ciclopirox. In this article, the potential for efinaconazole 10% solution and its corresponding vehicle to induce delayed contact skin sensitization and skin irritation is evaluated.

**METHODS**

**Contact sensitization.** This was a single-center study of 239 healthy adult volunteers (aged 18–70) conducted to examine the potential of efinaconazole 10% solution and its vehicle solution to induce contact sensitization following repeated application to the skin. All subjects were exposed to applications of both test solutions. The study was divided into three phases: induction, challenge, and re-challenge (if required), following the methodology of Jordan and King. During the induction period, each subject had two application sites on their back, between the left scapula and the spinal midline and above the waist, designated for product/patch application. Nine repetitive applications of the test solutions [0.2ml (±0.02ml)] were applied to occlusive patches (Parke-Davis Readi Bandage, Kendall Healthcare, Mansfield, Massachusetts) on the same site over a period of three weeks. Patches applied on Mondays and Wednesdays were worn for 48 (+/- 4 hours); patches applied on Fridays were worn for 96 hours (+/- 4 hours). Following this induction period, subjects did not receive any application of the test solutions for approximately three weeks (17–24 days).

The subsequent challenge phase comprised one 48-hour occlusive patch application [0.2ml (±0.02mL)] to a naive site on the right side of the back between the right scapula and spinal midline, with assessments at 48, 72, and 96 hours after patch application. Subjects who exhibited skin reactivity suggestive of induced contact sensitization were then re-challenged for 48 hours with an occlusive and semi-occlusive patch (both 0.2mL (±0.02mL) applied to the left side of the subject’s back, between the left scapula and spinal midline, with assessments at 48, 72, and 96 hours post-patch application. Additionally, repeated daily open applications of the test solutions were performed to the antecubital fossa of either the left or right arm (3 times/day for four days), with assessments at 24, 48, 72, and 96 hours after the first rub-in application.

The primary measure of contact sensitization induction was determined through assessments of the application sites during the challenge and re-challenge phases. Signs of dermal reactions were graded using a 6-point grading scale (Table 1). At the end of the challenge period, the investigator assessed the occurrence of any induced contact allergic reactions. Other local reactions and adverse events were reported individually.

**21-Day Cumulative Irritation.** The 21-Day Cumulative Irritation procedure, originally introduced by Lamman et al., has been successfully employed as a predictive test for comparing the irritation potential of mild to moderately irritating topically applied skin care products. The study was a single-center, test-site, randomized assessment in 37 healthy adult volunteers (aged 18–65) to evaluate the irritation potential of three concentrations of efinaconazole solution (1%, 5%, and 10%), its vehicle solution, and both positive [0.2% sodium lauryl sulfate (w/v in deionized water)] and negative (deionized water) controls, following daily occlusive patch applications (Monday–Friday) over a three-week period. Patches applied on Friday were kept on until the following Monday. The test articles (approximately 0.2mL) were applied to occlusive patches (Parke-Davis Bandages, Kendall Healthcare) and patches were applied on the same spot every day across the upper back for a subject. The location of the spot on the back was randomized across the 35 subjects. If a subject showed a score of 3 for two consecutive visits, the corresponding test article was discontinued and the last score was carried forward. Each test site was evaluated for signs of irritation, pruritus, burning and stinging, and tape reaction.

A Total Cumulative Irritation Index (CII) for each subject was calculated by summing each of the individual subject’s scores over the 21 evaluation days. The Mean

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**TABLE 1. Grading scale for contact sensitization response**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DEFINITION (IRRITATION SIGNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None (no evidence of any effect)</td>
</tr>
<tr>
<td>0.5</td>
<td>Barely perceptible (minimal, faint, uniform or spotty erythema)</td>
</tr>
<tr>
<td>1</td>
<td>Mild (pink, uniform erythema with or without edema, covering most of the contact site)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (pink-red erythema with or without edema, uniform in the entire contact site)</td>
</tr>
<tr>
<td>3</td>
<td>Marked (bright-red erythema with or without edema, petechiae, or papules)</td>
</tr>
<tr>
<td>4</td>
<td>Severe (deep-red erythema with or without edema, vesiculation, or weeping)</td>
</tr>
</tbody>
</table>
Cumulative Irritancy Index (MCII), a primary endpoint, was calculated as the sum of all subjects’ total irritation scores for the test solutions divided by 777 (15 evaluations x 37 subjects).

Local tolerability was evaluated by subjective assessments of the application sites. Observed responses (e.g., erythema) were graded according to a 4- to 5-point scoring scale (Table 2).

**RESULTS**

**Contact sensitization.** Two hundred seven subjects completed this study (mean age 43.3 years). The majority of subjects were women (58.9%) and most were Caucasian (52.2%). Three subjects went on to complete the rechallenge phase.

During the induction and challenge phases, efinaconazole 10% solution produced a patch test irritancy response score of 0 (barely any evidence of effect) or 0.5 (minimal, faint, uniform or spotty erythema) in the majority of subjects (67.8% and 91.6%, respectively), with a worst score of 3 observed in two subjects (1%) (Table 3). Vehicle solution also produced a response score of 0 or 0.5 in the majority of subjects (71% and 95%, respectively), with a worst score of 3, observed in four subjects (2%). The type of reported reactions included erosion, mild dryness, moderate dryness, mild edema, moderate edema, fissuring, glazing, mild hyperpigmentation, crusting/scabbing, mild papular response, pustule formation, vesicle formation, and/or peeling in test subjects during the induction and/or challenge phases of the study.

The reactivity observed with efinaconazole 10% solution and vehicle was not considered evidence of induced contact sensitization in 99.5% (206/207) and 99.0% (205/207) of subjects, respectively. However, three subjects (efinaconazole 10% solution [n=1] and vehicle [n=2]) exhibited reactivity, which required further evaluation in the rechallenge phase. The rechallenge procedure was conducted on these three subjects. There was no evidence of induced contact sensitization under occlusive, semi-occlusive, and open (open rub-in) applications of efinaconazole 10% solution. However, the skin reactivity observed with vehicle was probably allergic in nature under occlusive testing conditions. No meaningful skin reactivity was observed under semi-occlusive or open application.

Of the 239 subjects enrolled in the study, 23 non-serious adverse events (nsAEs) were recorded during the course of the study. Only one AE (burning sensation) was possibly related to study medication. There were five serious adverse events (sAEs) recorded during the study. All were unrelated to study medication.

**21-Day Cumulative Irritation.** Of the 37 subjects who completed this study, the majority were women (86%) and were Caucasian (43%), with a mean age of 42.7 years. Mean cumulative irritation scores for each test article are shown in Table 4.

Efinaconazole 1%, 5%, and 10% solution exhibited mean calculated cumulative irritancy indices (based on erythema
scores) of 1.12, 1.26, and 1.18, respectively, and were comparable to vehicle solution (1.04). By comparison, mean cumulative irritancy indices for 0.2% sodium lauryl sulfate and deionized water were 2.77 and 0.30, respectively (Figure 1). Overall, 70.5 percent of subjects reported "no" or "mild" erythema with efinaconazole 10% solution. Scores for pruritus, burning, and stinging were similar across all concentrations of efinaconazole solution (range 0.38-0.51 and 0.22-0.25, respectively), vehicle (0.47 and 0.37, respectively), and negative control. All test articles showed similar responses to tape reaction (range 0.61-0.76) (Figure 1).

**DISCUSSION**

Onychomycosis is a chronic, often refractory disorder, most commonly caused by a dermatophyte (T. rubrum, T. mentagrophytes). Long-term management is often required, especially with topical therapy, and eradication of

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**TABLE 3. Frequency (%) of erythema scores with efinaconazole 10% solution and vehicle (induction and challenge phase)**

<table>
<thead>
<tr>
<th>CLINICAL SCORE</th>
<th>INDUCTION</th>
<th></th>
<th>CHALLENGE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EFINACONAZOLE 10% SOLUTION</td>
<td>VEHICLE</td>
<td>EFINACONAZOLE 10% SOLUTION</td>
<td>VEHICLE</td>
</tr>
<tr>
<td>0</td>
<td>30.2%</td>
<td>35.9%</td>
<td>56.2%</td>
<td>65.7%</td>
</tr>
<tr>
<td>0.5</td>
<td>37.6%</td>
<td>34.9%</td>
<td>35.4%</td>
<td>28.0%</td>
</tr>
<tr>
<td>1</td>
<td>27.7%</td>
<td>25.9%</td>
<td>8.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>2</td>
<td>4.3%</td>
<td>3.2%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**TABLE 4. Mean cumulative irritation scores for efinaconazole solution (1%, 5%, and 10%), solution, vehicle, and positive/negative controls**

<table>
<thead>
<tr>
<th>TEST ARTICLE</th>
<th>CUMULATIVE IRRITATION</th>
<th>PRURITUS</th>
<th>BURNING/STINGING</th>
<th>TAPE REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efinaconazole 1% solution</td>
<td>1.12</td>
<td>0.51</td>
<td>0.22</td>
<td>0.70</td>
</tr>
<tr>
<td>Efinaconazole 5% solution</td>
<td>1.26</td>
<td>0.38</td>
<td>0.23</td>
<td>0.70</td>
</tr>
<tr>
<td>Efinaconazole 10% solution</td>
<td>1.18</td>
<td>0.48</td>
<td>0.25</td>
<td>0.76</td>
</tr>
<tr>
<td>Efinaconazole vehicle solution</td>
<td>1.04</td>
<td>0.47</td>
<td>0.18</td>
<td>0.69</td>
</tr>
<tr>
<td>0.2% sodium lauryl sulfate*</td>
<td>2.77</td>
<td>0.68</td>
<td>0.38</td>
<td>0.61</td>
</tr>
<tr>
<td>Deionized water</td>
<td>0.30</td>
<td>0.37</td>
<td>0.18</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Tested as a 0.2% aqueous dilution (w/v in deionized water)
the fungal pathogen is difficult to achieve. The aim is to eradicate the pathogen, allow a healthy nail to grow in and replace the previously infected nail plate, and reduce the risk of recurrence. Any long-term management program demands good patient adherence, and with onychomycosis, this is particularly challenging. The ideal topical product should not cause irritant or allergic contact dermatitis. These side effects are likely to adversely affect patient adherence.

The most common adverse events with current topical treatments are periungual erythema and erythema of the proximal nail fold. These occur in about five percent of patients treated with ciclopirox.10 In addition, sporadic cases of contact sensitization have been reported with ciclopirox.14,15

The evaluations reported here showed that efinaconazole 10% solution did not cause contact sensitization. In addition, all concentrations of efinaconazole solution (1–10%) exhibited only minimal skin irritation.

The completed Phase 2 and 3 clinical program with efinaconazole 10% solution in mild-to-moderate onychomycosis will provide additional insights into the tolerability of this new topical treatment for onychomycosis.

ACKNOWLEDGMENT

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