Drugs 1998 Mar; 55 (3): 405-412
0012-6667/98/0003-0405/$08.00/0

Butenafine

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Contents

Summary

▲ Butenafine is a new antifungal agent with primary fungicidal activity against dermatophytes such as *Trichophyton mentagrophytes*, *Microsporum canis* and *Trichophyton rubrum* which cause tinea infections.

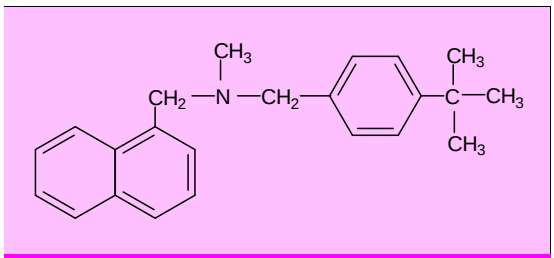
▲ ^{14}C-labelled butenafine (≈30 μg/g tissue) was found within guinea-pig dorsal skin 24 hours after topical application. Most of the drug was distributed into the epidermis including the horny layer. Small amounts were found in the dermis, probably transported via sebaceous glands and hair follicles.

▲ *In vitro*, the minimum concentration that completely inhibited growth of dermatophytes (MIC) and the minimum fungicidal concentrations (MFC) for butenafine against *T. mentagrophytes* and *M. canis* were similar (0.012 to 0.05 mg/L) and were 4 to 130 times lower than those for naftifine, tolnaftate, clotrimazole and bifonazole. It also has greater activity against *T. rubrum*, *M. gypseum* and *Epidermophyton floccosum* when compared with naftifine, tolnaftate and clotrimazole; comparisons with bifonazole against these strains were not available.

▲ Assessment after 1 week's treatment in patients with tinea pedis revealed that mycological cure rates were greater in those who received twice-daily butenafine for 1 week or once-daily butenafine for 4 weeks than in placebo recipients. Mycological and overall cure rates were either further increased or maintained up to 5 weeks after treatment cessation compared with end-of-treatment values.

▲ In patients with tinea cruris or tinea corporis who received once-daily butenafine 1% for 2 weeks, the mycological and overall cure rates continued to increase for up to 4 weeks after treatment cessation.

Features and properties of butenafine (KP 363)	
Indications	
Tinea infections	Focus of this profile
Other mycoses	
Mechanism of action	
Antifungal	Fungal squalene epoxidase inhibitor
Dosage and administration	
Usual dosage in clinical trials	1% cream
Route of administration	Topical
Duration and frequency of treatment	Tinea pedis 1wk twice daily *or* 4wk once daily
	Tinea cruris and corporis 2wk once daily
Pharmacokinetic profile	
Mean plasma concentration after 14 days' treatment with once-daily 1% cream	0.91 μg/L
Adverse events	
Most frequent	Mild burning at application site in ≤2% of patients



Butenafine

Superficial fungal infections are common world-wide. Three main anamorphic genera of dermatophyte are responsible for the group of infections known as tinea:[1] *Trichophyton, Microsporum* and *Epidermophyton. Trichophyton rubrum* and *Trichophyton mentagrophytes* are the main cause of tinea pedis, and *T. rubrum, T. mentagrophytes* and *Epidermophyton floccosum* are the main cause of tinea cruris. Tinea infections affect the keratinised cells of the skin, hair and nails and are named according to the anatomical site infected. These infections are contagious and are transmitted via physical contact with arthroconidia, which are generated from dermatophyte filaments. Because arthroconidia can survive for years embedded in scales of hair and skin, recurrent outbreaks of infection may occur, particularly in individuals with a compromised immune system.[1]

Several classes of antifungal agents including imidazoles, triazoles and allylamines are available.[1] The first two classes interfere with fungal 14α-demethylase, which is dependent on cytochrome P450, and inhibit the formation of ergosterol. These agents may also interfere with the human cytochrome P450 system causing unwanted toxicity. Allylamine agents inhibit squalene epoxidation and do not interfere with cytochrome P450–dependent enzymes.

In the clinical setting, use of fungistatic agents such as topical azole compounds may lead to rapid relapse and/or incomplete eradication of the infecting organism when treatment is withdrawn. Inhibition of fungal squalene epoxidation is thought to confer fungicidal activity.[2] Butenafine, a fungicidal agent, is the first representative of a new class of antifungal agents; it is a benzylamine derivative with a chemical structure and a mode of action similar to the allylamine class of antifungal agents.[3]

1. Pharmacodynamic Profile

- Fungistatic activity was defined as the lowest concentration that completely inhibited *in vitro* growth of dermatophytes (MIC). The minimal fungicidal concentration (MFC) was defined as the lowest concentration that prevented visible growth when subcultured on to agar plates.[4] The MFC values of butenafine against *T. mentagrophytes* and *Microsporum canis* were 4 to 130 times lower than those of naftifine, tolnaftate, clotrimazole or bifonazole; the MIC values were 4 to 65 times lower than those of the same comparator drugs (fig. 1). The MIC and MFC values for butenafine against *T. mentagrophytes* were the same (0.012 mg/L) and those against *M. canis* were similar (0.025 and 0.05 mg/L, respectively) suggesting that the activity against these organisms is essentially fungicidal (fig. 1\).

- *In vitro*, geometric mean MIC values for butenafine were lower than those for naftifine, tolnaftate or clotrimazole against clinical isolates of dermatophytes including *T. mentagrophytes*, *T. rubrum*, *M. canis*, *M. gypseum*, and *E. floccosum* incubated on Sabouraud's dextrose agar medium, at 27°C for 7 days (fig. 2).[5] These data indicate a broad spectrum activity for butenafine which is more potent than the comparator agents.

- *In vitro*, MIC values against clinical isolates of *T. rubrum* ranged from 0.007 to 0.015 mg/L 48 hours after initial inoculation and were 0.015 mg/L at 72 hours after inoculation;[6] corresponding minimum lethal concentrations (MLC; the lowest concentration which resulted in growth of ≤5 colonies) were 0.015 mg/L and 0.015 to 0.125 mg/L.

- In the guinea-pig dorsal skin trichophytosis model, butenafine was 65 times more fungicidal and 33 times more fungistatic than clotrimazole against arthroconidia of *T. mentagrophytes*:[4] MFC values were 0.012 and 0.78 mg/L for butena-

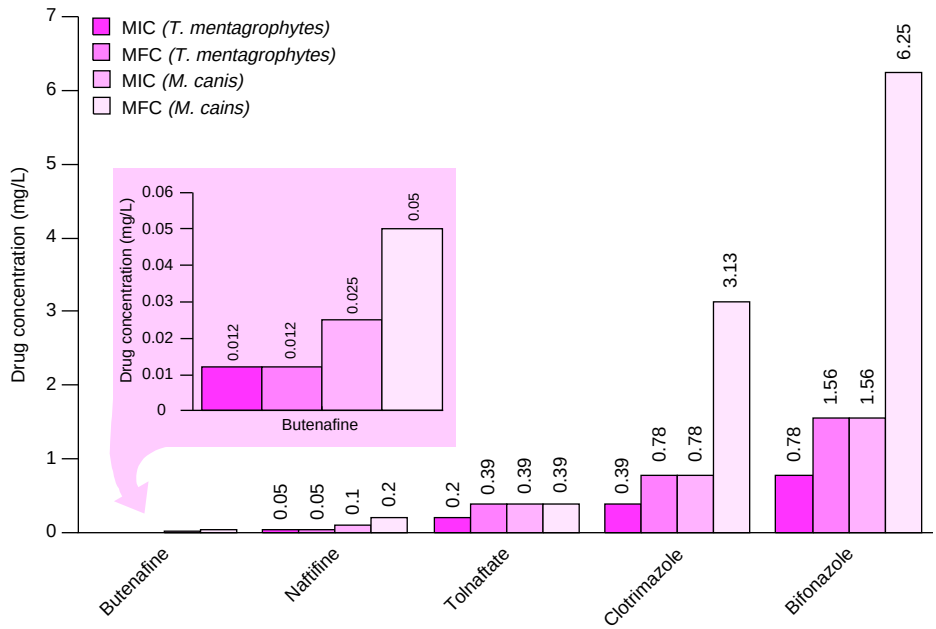


Fig. 1. *In vitro* fungistatic and fungicidal activities of butenafine and comparator drugs against *Trichophyton mentagrophytes* and *Microsporum canis*. Fungistatic activity was measured as the minimum concentration (MIC) of the drug that completely inhibited growth of dermatophytes. Fungicidal activity was measured as the minimum fungicidal concentration (MFC) that prevented visible culture growth when subcultured onto agar plates.[4] The insert is for clarification and shows more clearly the identical or similar MIC and MFC values of butenafine against these organisms, illustrating its primary fungicidal property.

fine and clotrimazole; corresponding MIC values were 0.012 and 0.39 mg/L. The size of the inoculum did not affect the antifungal activity of butenafine.[7] Negative cultures were seen in 100% of skin sections infected with 10^4, 10^5 or 10^6 cells per lesion. Conversely, the effect of clotrimazole was reduced with increasing inoculum size: 98, 46 and 20% of cultures, respectively, were negative for 10^4, 10^5 and 10^6 cells per lesion.

- In a comparative study, 10 days after the planta of the hind paw of guinea-pigs was inoculated with *T. mentagrophytes*, a variety of antifungal agents (1% cream formulation) were applied once daily for 20 days.[8] Butenafine caused a significantly greater mycological eradication than bifonazole or clotrimazole: respective negative cultures were 88.5, 31.3, and 27.1% ($p < 0.001$)

- Interdigital tinea pedis was induced in guinea-pigs by inoculation with *T. mentagrophytes*.[9] After 20 days' application of butenafine 1% cream, bifonazole 1% cream or no treatment, 8.3, 44.2 and 97.5%, respectively, of skin sections taken from infected areas had positive cultures ($p < 0.05$ *vs* untreated group). Post-application assessment of fungal growth, 30 days after drug cessation revealed that butenafine, compared with bifonazole or no treatment, prevented relapse of interdigital tinea pedis: negative cultures were seen in 75% of samples from the butenafine group, 8.3% from the bifonazole group and 0% from the nontreated group ($p < 0.05$ *vs* bifonazole and untreated groups).

- Topical butenafine 1% solution (0.2ml) applied once 24 or 48 hours before fungal inoculation with *T. mentagrophytes* in guinea-pigs (dorsal skin) completely prevented mycological infection for up to 17 days; pretreatment 72 hours before inocula-

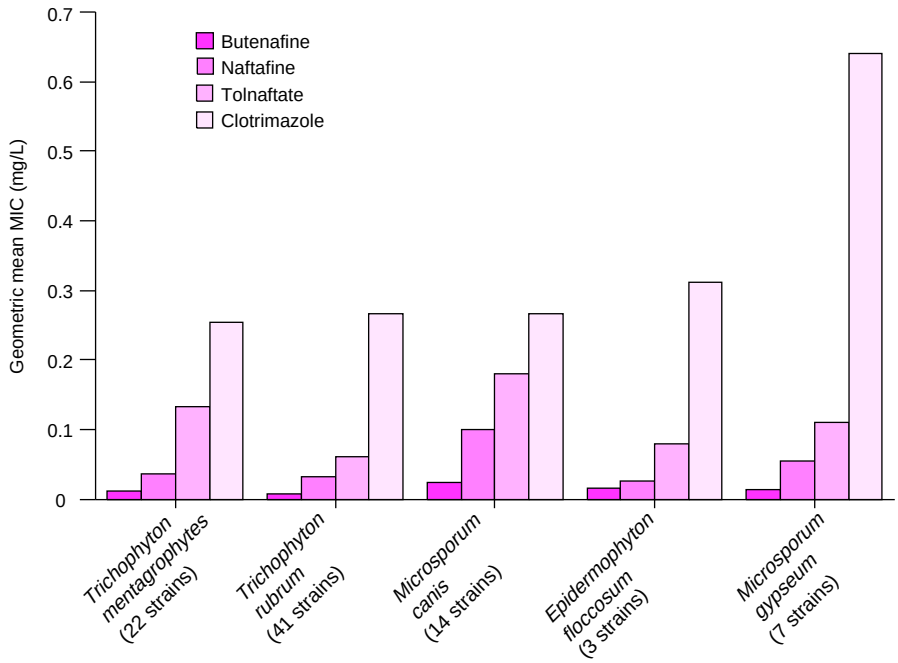


Fig. 2. *In vitro* antifungal activity of butenafine and comparator agents measured as minimum concentration (MIC) that completely inhibited growth of clinical isolates of dermatophytes.[5]

tion prevented infection in 60% of the animals over the same period.[4]

• *In vitro* (cell culture) studies have shown that butenafine is active against *Candida albicans* and that the effect is probably the result of direct action on the membrane structure of the organism rather than an alteration in the cellular sterol composition.[10]

• Inhibition of fungal squalene epoxidation causes the antifungal action of butenafine against susceptible fungi such as *Sporothrix schenckii*.[11]

2. Pharmacokinetic Profile

• Skin permeation of the drug was assessed in guinea-pigs after topical application (24-hour duration[12]) of 0.2ml of a 1% solution of ^{14}C-labelled butenafine.[7] The highest concentration of radioactivity (estimated as 250 to 500μg of butenafine per gram of tissue) was found in the epidermis, including the horny keratinised layer (0 to 50μm deep). Here, the radioactive concentration reached a plateau 1 to 2 days after application and remained constant for up to 7 days. Low concentrations of radioactivity were also located at the level of the sebaceous glands (100 to 300μm) and the hair follicles (1300 to 1600μm), suggesting penetration to the deeper layers of the dermis via these 2 structures.

• In guinea-pigs (n = 5) the concentration of butenafine in the skin 24 hours after application of 2mg of the agent (0.2ml of a 1% solution) was 31.5 μg/g tissue; at 72 hours *post* application it was 8.8 μg/g tissue.[4] *In vitro* concentrations required for fungicidal activity against *T. mentagrophytes* and *M. canis* were between 0.012 and 0.05 mg/L.

• In patients with tinea cruris who applied butenafine 1% cream once daily, the mean plasma concentration of the drug after a 14-day treatment period was 0.91 μg/L.[13] This suggests poor sys-

temic distribution of the drug after topical application. Five weeks after treatment termination, mean butenafine plasma concentrations were between 0.15 and 0.28 μg/L in 5 of 17 patients.

3. Therapeutic Trials

Several primary end-points were used to assess the efficacy of butenafine in clinical trials:

- Mycological cure: negative fungal culture and potassium hydroxide (KOH) test.
- Effective treatment: mycological cure and investigator global assessment of 'cleared' (100% remission) or 'excellent' (80 or 90 to 99% improvement).
- Overall cure: mycological cure and investigator global assessment of 'cleared'.

Where specified in the literature reviewed, the most common causative pathogen was *T. rubrum*.[13-16]

- In a double-blind trial, butenafine 1% cream applied twice daily for 7 days (n = 132) produced a significantly higher mycological cure rate than vehicle (n = 139) as early as day 8 in patients with tinea pedis (43 *vs* 25%; p = 0.021).[14] This rate continued to increase in both groups to day 14 (61 *vs* 35%; p < 0.0001) and was further increased up to 5 weeks after treatment cessation (day 42) in the butenafine group, but declined in vehicle recipients (74 *vs* 22%; p < 0.0001) [fig. 3]. The effective treatment rate followed a similar temporal pattern: for butenafine and vehicle recipients, respectively, the rates were 6 and 1% at day 8 (p = 0.017), 17 and 9% at day 14 (p = 0.045) and 40 and 9% at day 42 (p < 0.0001). The overall cure rate was significantly better in butenafine than vehicle recipients at day 14 (4 *vs* 0%; p = 0.026), and was further increased in the butenafine group but essentially unchanged in the vehicle group at day 42 (20 *vs* 1%; p < 0.0001).

- In a smaller double-blind trial, patients with tinea pedis applied either butenafine 1% cream (n = 40) or vehicle (n = 40) once daily for 4 weeks.[15] After 1 week, mycological cure was achieved in 40% of butenafine recipients and 20% of vehicle recipients (p = 0.081[17]). Corresponding mycological cure rates after 4 weeks' therapy were 88 and 45% (p < 0.001[17]); these rates were maintained in butenafine recipients, but declined (to 33%; p < 0.001[17]) in vehicle recipients 4 weeks after treatment cessation (week 8). The overall cure rate was significantly greater in butenafine than vehicle recipients at week 8 (23 *vs* 5%; p = 0.012).

- Butenafine 1% cream (n = 37) or vehicle (n = 39) was applied once daily for 2 weeks by patients with tinea cruris.[13] Mycological cure, seen as early as day 7, occurred in 66 and 13% of butenafine and placebo recipients (p < 0.0001). The cure rate was greater in butenafine than in vehicle recipients throughout the 2-week treatment phase and the 4-week post-treatment period. At day 42, mycological cure rates were 81% for butenafine and 13% for vehicle recipients (p < 0.0001). Overall cure rates at day 14 were 32% for butenafine and 8% for vehicle recipients (p < 0.01). At day 42, this rate was increased in butenafine recipients and decreased in vehicle recipients (62 *vs* 3%; p < 0.0001), suggesting a prolonged post-treatment effect of the active agent (fig. 4).

- In another trial that did not include a follow-up period to assess further disease resolution after

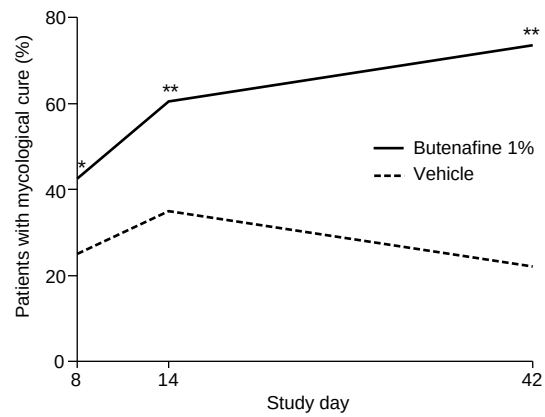


Fig. 3. Mycological cure (negative fungal culture and potassium hydroxide test) after treatment cessation in patients with tinea pedis who received vehicle (n = 139) or butenafine 1% (n = 132) twice daily for 7 days.[14] Assessments were made on days 8, 14 and 42. *Symbols:* * p = 0.012, ** p < 0.001 *vs* vehicle.

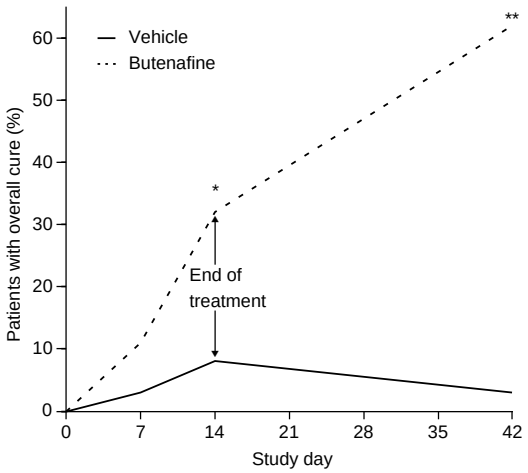


Fig. 4. Prolonged therapeutic effect of butenafine 1% cream once daily for 14 days in 76 patients with tinea cruris. Efficacy was assessed by 'overall cure' rate [negative potassium hydroxide test and mycological culture plus investigator global response assessment of 'cleared' (100% remission)].[13] *Symbols:* * $p < 0.01$, ** $p < 0.0001$ *vs* vehicle.

treatment cessation, results from 36 evaluable patients with tinea pedis indicate that once-daily butenafine 1% cream and twice-daily clotrimazole 1% cream may have similar therapeutic potential after 4 weeks' application.[18] Pathogenic eradication rates were 94.7% for butenafine and 88.2% for clotrimazole recipients. Final overall evaluation of skin findings was 'moderately or markedly improved' in 78.9% of butenafine and 76.5% of clotrimazole recipients; final overall effect was 'good or excellent' in 84.2% of butenafine and 82.4% of clotrimazole recipients. However, the lack of follow-up did not allow assessment of the potential for a continued effect of each drug after treatment cessation.

• In a double-blind trial patients with tinea corporis received either butenafine 1% cream (n = 42) or cream vehicle (n = 36) once daily for 2 weeks.[16] Mycological cure was significantly greater in butenafine than in vehicle recipients at day 7 (64 *vs* 9%; $p < 0.0001$), at day 14 (88 *vs* 28%; $p < 0.0001$) and at day 42, 4 weeks after treatment cessation (88 *vs* 17%; $p < 0.0001$). Effective treatment rates were also higher at all time points in butenafine than in vehicle recipients: 33 *vs* 0%, 60 *vs* 17%, and 81 *vs* 14%, respectively, for days 7, 14 and 42 (all $p < 0.0001$). Compared with vehicle recipients, patients receiving butenafine had a significantly higher overall cure rate by day 14 (31 *vs* 3%; $p < 0.001$) which improved by day 42 (67 *vs* 14%; $p < 0.0001$).

• The continuous clinical response to butenafine after treatment cessation was reflected by the investigator's global assessment: in patients with tinea corporis an assessment of 'cleared or excellent' was reported in significantly more butenafine 1% than placebo recipients after 14 days' once-daily application (64 *vs* 25%; $p < 0.001$);[16] the condition was reported as 'worse' in 14% of placebo recipients and none of those who received butenafine ($p < 0.001$; fig. 5). Five weeks after treatment cessation butenafine was increasingly more effective than placebo: 85% of butenafine and 20% of placebo recipients had a 'cleared or excellent' response, and 28% of placebo recipients and none of the butenafine recipients were 'worse' ($p < 0.0001$).

• Similarly, at the end of 4 weeks' once-daily treatment in 80 patients with tinea pedis an assessment of 'cleared or excellent' was reported in 68% of butenafine 1% and 40% of placebo recipients.[15] Four weeks after treatment cessation (week 8), an assessment of 'cleared or excellent' improved to 78% in butenafine recipients, but reduced (to 35%) in those receiving placebo.

4. Tolerability

• Butenafine appears to be well tolerated when applied topically. In 2 separate studies, 1 of 46[13] and 1 of 197[14] patients with tinea pedis who received butenafine 1% cream reported mild burning and/or stinging on application. In the latter study,[14] 3 of 196 vehicle recipients also reported mild burning on application and 1 other had elevated aspartate and alanine aminotransferase levels. There were no withdrawals from either study. In a third trial,[15] mild burning at the application

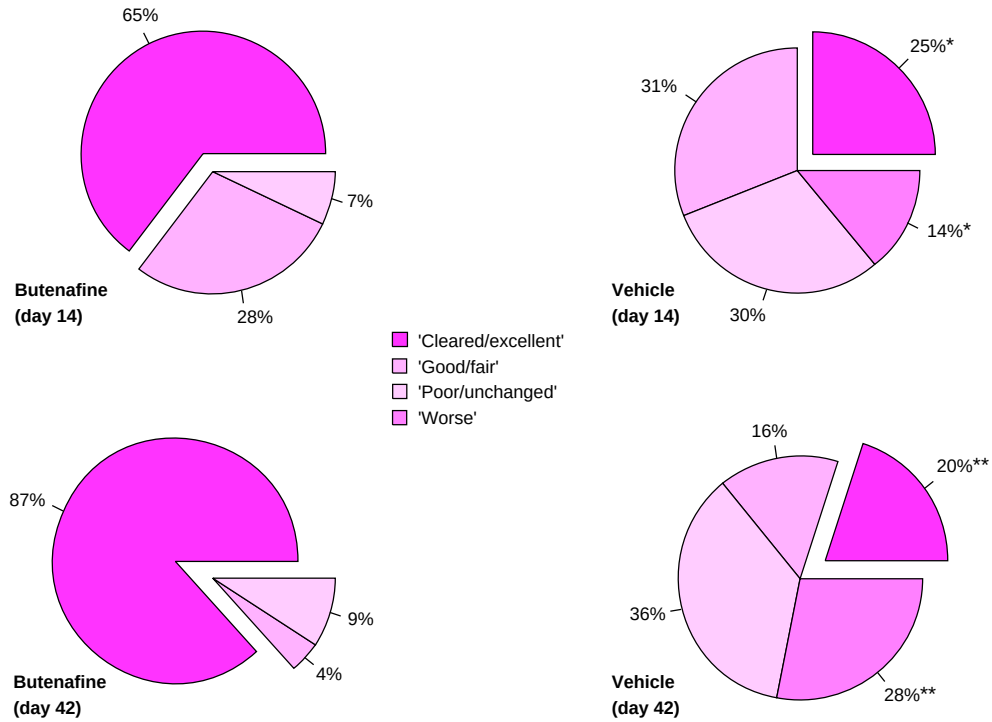


Fig. 5. Investigators' global assessment of clinical response to butenafine 1% or placebo once daily for 14 days in patients (n = 78) with tinea corporis.[16] Assessments were made at the end of the treatment period (day 14) and 4 weeks after treatment cessation (day 42) and were scored as follows: cleared or excellent (90 to 100% improvement), good or fair (25 to 89% improvement) poor (<25% improvement). *Symbols:* * $p < 0.001$, ** $p < 0.0001$ *vs* butenafine.

site was reported by 1 of 60 butenafine recipients and 4 of 59 vehicle recipients, 1 of whom withdrew from the study. An additional vehicle recipient had a high serum lactate dehydrogenase level in week 8 (creams were applied for 4 weeks), which returned to within normal levels 4 weeks later.

- A skin patch test, judged on a 6-point scale defined according to the Japan Investigational Group criteria, was carried out in 36 healthy volunteers.[19] Test preparations of 0.5% cream and 0.1% solutions of butenafine and a number of antifungal agents were compared. Positive patch test rates (assumed skin irritation) were observed as follows: 8.3% (econazole solution), 5.6% (econazole cream), 2.8% (tolciclate cream) and 0% (butenafine cream and solution, bifonazole cream and solution). These data suggest butenafine has a low potential for skin irritation.

5. Butenafine: Current Status

Butenafine is a fungal squalene epoxidase inhibitor that has been launched in some countries including Japan and the US for use in tinea infections. In short term clinical trials (≤4 weeks) butenafine was effective against tinea pedis, tinea cruris and tinea corporis; mycological efficacy was maintained during follow-up periods of up to 5 weeks after treatment cessation. The agent was well tolerated; the most commonly occurring adverse event was mild burning at the application site. This was reported more frequently in vehicle

(1.5 to 7%) than in butenafine (0.5 to 2%) recipients.

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