Lamisil Once 1% film forming cutaneous solution – Terbinafine 1% FFS

"The only treatment that treats and prevents Athlete's Foot with just one application"

Claim substantiation concerning treatment:

Terbinafine, the active ingredient in Lamisil Once 1% FFS, is an allylamine and has fungicidal action against many types of fungi i.e. it kills these fungi [1, 2]. In vitro susceptibility tests have shown that terbinafine has primarily fungicidal activity against dermatophytes, Aspergillus species, Scopulariopsis brevicaulis, Blastomyces dermatitidis, Histoplasma capsulatum and Candida parapsilosis, but only fungistatic activity against Candida albicans [3].

Tinea pedis is most commonly caused by the dermatophytes Trichophyton rubrum and Trichophyton interdigitale (formerly T. mentagrophytes var. interdigitale) [4].
Ergosterol is an essential component of virtually all fungal cells as it is required for membrane integrity and also for growth. Most antifungal agents interfere with ergosterol either by directly inhibiting its biosynthesis (allylamines, azoles, morpholines, thiocarbamates) or by interacting with it in the cell membrane (polyenes) [1]. Terbinafine, like other allylamines, specifically inhibits fungal ergosterol biosynthesis at the point of squalene epoxidation. As a result, treated fungal cells rapidly accumulate the intermediate squalene and become deficient in the end-product of the pathway, ergosterol. The gradual onset of fungal cell death is believed to be primarily due to accumulation of high levels of intracellular squalene, probably in combination with ergosterol deficiency [1].

Most topical treatments for fungal skin infections contain an *azole* active ingredient like for example clotrimazole, miconazole or ketoconazole. Azoles inhibit the production of ergosterol further down the synthesis pathway than terbinafine and do not result in the build-up of high levels of squalene. Azoles inhibit the biosynthesis of ergosterol reducing bioavailability and slowing down reproduction therefore inhibiting growth. Azoles therefore are fungistatic [2].

Several multicentre, randomized, double-blind and placebo-controlled clinical trials with Lamisil Once 1% FFS provide evidence for effectively treating tinea pedis with one single application: two Phase III pivotal studies [6,7] and a Phase II dose finding study [8].

A multicentre, randomized, double-blind, placebo-controlled clinical trial with Lamisil Once 1% FFS was conducted in a total of 273 subjects (12 years and older) with interdigitale type tinea pedis with possible extension to the lateral surfaces and soles of the feet [6]. Subjects were instructed to apply treatment once only between, under and over the toes, sole and sides of both feet, even if the skin of one foot looked healthy. They were to avoid washing their feet for 24 h after application of the study medication.

After 1 and 6 weeks, subjects were evaluated for clinical response, and after 12 weeks for evaluating relapse/re-infection of subjects effectively treated at week 6. The primary efficacy endpoint was rate of *effective treatment* at week 6, defined as mycological cure (negative microscopy and culture), plus absent or minimal signs and symptoms; mild or no erythema, desquamation or pruritus (individual scores ≤1), no pustules, incrustation or vesiculation, and a total sign/symptom score ≤2_. Secondary efficacy endpoints included *mycological cure* and changes in *clinical signs/symptoms score*, evaluated at weeks 1 and 6.

Effective treatment: At week 6, effective treatment rate in Lamisil Once 1% FFS group was 63.2% (120/190) and significantly higher compared with 16.9% (14/83) in subjects in vehicle group ($p<0.0001$).

Mycological cure: At week 6, mycological cure was achieved in 71.6% (136/190) of subjects in Lamisil Once 1% FFS group compared with 20.5% (17/83) of subjects in vehicle group (p<0.0001).

Clinical signs/symptoms score: Among subjects in Lamisil Once 1% FFS group, mean total signs and symptoms score decreased from 5.9 at baseline to 3.2 at week 1 and 1.3 at week 6. In the vehicle group these values were 6, 3.6 and 3.4, respectively. The difference between treatments at week 6 was significant (p<0.0001) [6].

Another multicentre, randomized, double-blind, placebo-controlled clinical trial with Lamisil Once 1% FFS was conducted in in total 290 adult Chinese subjects with interdigitale type tinea pedis with possible extension to the lateral borders of foot and sole [7]. Investigator applied treatment to the affected foot (feet) on Day 1. After 1 and 6 weeks, subjects were evaluated for clinical response. The primary efficacy endpoint was rate of *effective treatment* at week 6, defined as in [6]. Secondary efficacy endpoints included *mycological cure* and *total clinical signs and symptoms score* evaluated at weeks 1 and 6.

Effective treatment: At week 6, effective treatment rate in Lamisil Once 1% FFS group was 63.5% (73/115) and significantly higher compared with 8.2% (10/122) in subjects in vehicle group (p<0.001).

Mycological cure: At week 6, mycological cure was achieved in 86.1% (99/115) of subjects in Lamisil Once 1% FFS group compared with 12.3% (15/122) of subjects in vehicle group (p<0.001).

Clinical signs/symptoms score: At week 1, the average total signs and symptoms scores were similar; 4.2 in the Lamisil Once 1 % FFS group and 4.8 in the vehicle group, but statistically significantly different (p=0.005). At week 6, the average signs and symptoms score for Lamisil Once 1 % FFS group was much lower compared with vehicle group; 1.6 vs 4.7, respectively (p<0.001) [7].

Further evidence provides a dose finding multicentre, randomized, double-blind, placebo-controlled clinical trial with Lamisil Once 1% FFS, 5% FFS and 10% FFS in 344 subjects (12 years and older) with interdigitale type tinea pedis with possible extension to the lateral borders of the foot and sole [8]. The treatment was applied by investigator once on Day 1 to both feet, covering the four interdigital spaces, the sole and the lateral surfaces up to approximately 1.5 cm. After 1 and 6 weeks, subjects were evaluated for clinical response. The primary efficacy endpoint was rate of *effective treatment* at week 6, defined as in [6]. Secondary efficacy endpoints included *mycological cure* and *total clinical signs and symptoms score* evaluated at weeks 1 and 6.

Effective treatment: At week 6, effective treatment rate in Lamisil Once 1% FFS group was 66.4% and significantly superior to 17.8% in subjects in vehicle group. Effective treatment rates in 5% and 10% FFS groups were 69.7% and 61.3%, respectively.

Mycological cure: At week 6, mycological cure was achieved in 84.1% of subjects in Lamisil Once 1% FFS group and significantly superior compared with 26.7% of subjects in vehicle group. Mycological cure rates in 5% and 10% FFS groups were 79.8% and 82.8%, respectively.

Clinical signs/symptoms score: Among subjects in Lamisil Once 1% FFS group, mean total signs and symptoms score decreased from 5.4 at baseline to 2.9 at week 1 and 1.5 at week 6. In the vehicle group these values were 5.3, 2.6, 3.0, respectively. Corresponding mean total signs and symptoms score for 5% FFS group and 10% FFS group are 5.4, 2.9, 1.3 and 5.0, 2.7, 1.5, respectively.

Substantiation regarding prevention:

A multicentre, randomized, double-blind, placebo-controlled clinical trial with Lamisil Once 1% FFS was conducted in in total 273 subjects (12 years and older) with interdigitale type tinea pedis with possible extension to the lateral surfaces and soles of the feet [6]. Subjects were instructed to apply treatment once only between, under and over the toes, sole and sides of both feet, even if the skin of one foot looked healthy. After 1 and 6 weeks, subjects were evaluated for clinical response, and after 12 weeks for evaluating relapse/re-infection of subjects effectively treated at week 6.

Effective treatment: At week 6, effective treatment rate in Lamisil Once 1% FFS group was 63.2% (120/190) and significantly higher compared with 16.9% (14/83)in subjects in vehicle group ($p<0.0001$).

Relapse rate: In the Lamisil Once 1% FFS group, only 12.5% of subjects who were effectively treated at week 6 had a relapse/re-infection (positive culture) at week 12. Of the effectively treated subjects at week 6 in the vehicle group, 21% had a relapse/re-infection (positive culture) at week 12 [6]
A recurrence rate of 12.5% at week 12 is considered as low.

Substantiation for 'The only treatment with one application'

None of the other treatments available on the market provide treatment with just one application. There are a number of sprays, gels, creams and powders but they all require a course of treatment – normally being required to be applied at least once or twice a day for at least a week. Therefore Lamisil Once is the only treatment requiring one application.

References:

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