Brand Name: Luzu

Generic Name: luliconazole

Manufacturer[1]: Medicis Pharmaceutical Corporation

Drug Class[1,2,3,4]: Imidazole antifungal, topical

Uses

Labeled Uses[1,2,3,4]: Topical treatment of interdigital *tinea pedis*, *tinea cruris*, and *tinea corporis* caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum* in patients 18 years of age and older

Unlabeled Uses[2,3,4]: Currently there are no unlabeled uses listed for luliconazole

Mechanism of Action[1,2,3]:

Although the exact mechanism of action against dermatophytes is unknown, luliconazole appears to inhibit ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity by azoles results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol. This will lead to a disruption of normal fungal cell membrane permeability.

Pharmacokinetics[1,2,3,6]:

Absorption:

T_{max} (tinea pedis)	16.9 hours
T_{max} (tinea cruris)	21 hours
V_d	Not reported
$t_{½}$	19.9 hours
Clearance	Not reported
Protein binding	>99%
Bioavailability	Not reported

Metabolism: Not known

Elimination: Not known

Efficacy:

Watanabe S, Takahashi H, Nishikawa T. Dose-finding comparative study of 2 weeks of luliconazole cream treatment for tinea pedis – comparison between three groups (1%, 0.5%, 0.1%) by a multi-center randomized double-blind study. Mycoses. 2007; 50(1). 35-40.

Study Design: Multi-center, double-blind, randomized, parallel three-group design study

Description of Study: *Methods:* 241 patients, age 20-73 years, from 24 hospitals having *tinea pedis* (interdigital or plantar) were randomized to receive 1% (group A), 0.5% (group B) or 0.1% (group C) luliconazole cream once daily for 2 weeks. Evaluation of signs/symptoms and mycological testing (via KOH methods) were done at visit 1 (baseline) as well as weeks 2, 4, and 6. Cutaneous symptoms (pruritus, erythema, scaling) were assessed following a Likert scale and were compared versus the baseline visit to assess efficacy (0-25% of visit 1 score = markedly improved; 25-50% = moderately improved; 50-75% = slightly improved; 75%-100% = unchanged; >100% = aggravated). Dermal symptoms and mycological effects were examined separately and assessed as 1 = significantly improved dermal symptoms and disappearance of fungi; 2 = moderately improved dermal symptoms and disappearance of fungi; 3 = mildly improved dermal symptoms and no disappearance of fungi; 4 = unchanged dermal symptoms and no disappearance of fungi; and 5 = aggravated dermal symptoms and no disappearance of fungi. Adverse events, tolerability, and labs were examined at each visit. *Outcome Results:* 214 patients were evaluated for efficacy. Improvement of cutaneous symptoms (significantly improved and moderately improved only) showed high efficacy rates but were not statistically significant, and a plateau in efficacy was reached at week 4. A slight concentration-dependent tendency was observed with mycological effect in *tinea pedis*, but this was not statistically significant. There was also an "obvious" concentration-dependent relationship in the negative conversion rate of fungi for interdigital type. Results at week 2 for interdigital type suggest a difference between treatment groups as conversion rates were 81.1% (group A), 62.9% (group B), and 58.3% (group C) with P values of 0.079 (Fisher's exact test) and 0.038 (Mantel-Haenszel method). Mycological effect appeared to increase for the full 6 week trial. Overall clinical effects of those with assessments of 1 or 2 were as follows: week 2 – 52.7% (A), 44.8% (B), 45.1% (C); week 4 – 79.7% (A), 74.6% (B), 72.2% (C); week 6 – 87.8% (A), 94% (B), 88.9% (C); however no significant differences were found in overall clinical rates between groups. 224 patients were examined for safety. 2.6% of patients in group A had either eczema or contact dermatitis. 1.4% of patients in group B had pruritus. 2.6% of patients in group C had dyshidrotic eczema, erythema, or pain. All adverse reactions (2.6% of all patients) were mild in severity and occurred only at site of application.

Limitations: The study excluded patients with comorbidities such as diabetes. As this is a common disease state, the extrapolation of study data to many populations is limited. Patient demographics, while presented, were not assessed for statistical differences. Drastic differences in age between males and females in group A and C were noted (45 vs. 29 and 51 vs. 21, respectively) making baseline characteristics questionable. Most information on efficacies, including dose-dependent relationships, is presented as graphs without specific numbers or p-values to support claims of efficacy made in the text. No power is stated in this study making it impossible to determine if type 2 error is likely. The graphs referenced in the text are incorrect (e.g. Figure 1(b) is not mycological response rate as referenced in the text). Safety and adverse effects were not statistically analyzed. Compliance was an issue in the article resulting in no significant improvement; however, there was no mention of how this was assessed. Lab values were collected at each visit but receive no mention in reporting of safety or efficacy.

Conclusions: This study presents luliconazole as a safe and effective agent capable of clearing *tinea pedis* in half the time of other products (2 weeks rather than 4); however, these conclusions are based on loose data that is often not presented to the reader. Questionable demographics, improper statistical analysis, unfounded claims, and confusing reporting (e.g. errors in graphing) make this a less-than-reputable study. Further studies with proper reporting and analysis are necessary to adequately judge luliconazole's safety and efficacy.

Watanabe S, Takahashi H, Nishikawa T, et al. A comparative clinical study between 2 weeks of luliconazole 1% cream treatment and 4 weeks of bifonazole 1% cream treatment for tinea pedis. Mycoses. 2006; 49(3): 236-41.

Study Design: Multi-clinic, randomized, single-blind, parallel two-group design study

Description of Study: *Methods:* 511 patients, age 20-74 years, from 45 hospitals with *tinea pedis* (interdigital or plantar) were assigned via block randomization to either luliconazole cream 1% once daily for 2 weeks followed by placebo cream for 2 weeks or bifonazole cream 1% once daily for 4 weeks. Microscopy was used to test for mycological effect at weeks 1, 2, 3, and 4. Signs and symptoms (itching, erythema, erosion, scaling) were examined at the start of treatment and each follow-up visit and rated on a Likert scale (0 absent – 4 severe). These scores were compared with baseline to determine percent improvement of symptoms (0-25% of baseline symptoms = significantly improved; 25-50% = moderately improved; 50-75% = slightly improved; 75%-100% = unchanged; >100% = aggravated). The combination of symptom scores and mycological effect was used to determine the overall clinical effect. Patients with positive mycological testing at week 2 received a culture study. Adverse events and tolerability were assessed at each visit. Blood tests and urine tests were drawn at each visit. *Outcome Results*: 489 patients were analyzed. 305 patients had culture-confirmed dermatophyte infections at baseline. Assessment of efficacy of improvement of skin lesions (patients whose scores were "moderately improved" or better) at 4 weeks was 91.5% with luliconazole versus 91.7% with bifonazole (P= 1.000). Looking at each visit, the time frame of improvement of skin lesions was "nearly equal" between the two treatment groups (P = 0.5102). Mycological effect showed negative results of 76.1% in the luliconazole group versus 75.9% in the bifonazole group (no p-value). Again, a similar time to effect was noted between the treatment groups (P = 0.8294). 227 patients were KOH positive at the end of week 2. Cultures performed on this group saw 73% of patients in the luliconazole group were cultured negative versus 50% in the bifonazole group. Adverse effects and tolerability revealed no relevant differences between either treatment group (2.0% luliconazole vs. 2.4% bifonazole; no p-value).

Limitations: This study excluded patients with comorbidities such as diabetes and kidney impairment. As these are common disease states, this decision limits the extrapolation of the study data to many populations. Not all patients (305 out of 489) had culture-confirmed dermatophyte infections. This could diminish efficacy of both products as they could potentially be treating infection that are not fungal and therefore untreatable by these means. 511 patients entered this study; however, only 500 were used for safety analysis. Dropouts are not mentioned, and number of patients in efficacy tables

is not consistent. Baseline characteristics, along with data like adverse effects, were not statistically examined. Some data, such as the time frame of improvement of skin lesions or KOH study, is not presented in the text nor figures (in these cases, only a p-value is presented). Power was not mentioned in the study to determine superiority. Results presented are the end points of the study meaning the majority of the data collected at each visit is not reported. Labs and urine samples were collected at each visit but were only reported as adverse effects - if deemed drug-related - and were not used for efficacy analyses.

Conclusions: According to the authors, this study proves that short-term (2 week) application of luliconazole 1% cream exhibited superior efficacy in eradication of fungal infection when compared to 4 weeks of bifonazole 1% cream; however, these conclusions are questionable given the incomplete nature of the study. Unreported data, lack of adequate statistical analysis, exclusion of common patient populations (e.g. diabetes), and a baseline demographic who may not have had fungal infections to begin with make this study appear unbelievable for many of the claims it makes. More studies, with better design, are required to determine the head-to-head efficacy of luliconazole versus other medications.

Jerajani HR, Janaki C, Kumar S, et al. Comparative assessment of the efficacy and safety of sertaconazole (2%) cream versus terbinafine cream (1%) versus luliconazole (1%) cream in patients with dermatophytoses: a pilot study. Indian J Dermatol. 2013; 58(1). 34-8.

Study Design: Multicenter, randomized, open-label, parallel three-group design study

Description of Study: *Methods:* 83 patients, aged 18-70 years, with clinical diagnosis and mycological confirmation (positive KOH test) for *tinea corporis* or *tinea cruris* infection were randomized to receive sertaconazole 2% cream applied twice daily for 4 weeks, terbinafine 1% cream once daily for 2 weeks, or luliconazole 1% cream once daily for 2 weeks. At the end of this "treatment" phase, there was a "follow-up" phase 2 weeks later in which patients were assessed clinically and mycologically for relapse. Primary efficacy was based on clinical and mycologic assessment (via KOH mounting) of *tinea* lesion at baseline, end of treatment phase, and end of follow-up phase. Clinical assessment was based on symptoms of lesions (pruritus, erythema, etc.) and was graded on a 0-3 Likert scale (0 = none; 3 – severe). Secondary efficacy was a composite score of clinical symptoms and global assessment consisting of successful treatment outcome (clinical cure + negative mycology), clinical success (symptomatic relief + clinical cure) or clinical failure (no clinical and mycological improvement) at the end of the treatment and follow-up phases. Safety and tolerability were assessed at each visit. Intent-to-treat protocols were used. *Outcome Results:* 62 patients completed the study (6 lost in sertaconazole group and 7 each in the others). Changes in pruritus are as follows: treatment phase resolution -85% sertaconazole; 54.6% terbinafine; 70% luliconazole – follow-up phase resolution – 100% sertaconazole/luliconazole; 95.5% terbinafine. Resolution of erythema: treatment phase – 95% sertaconazole; 90.9% terbinafine; 85% luliconazole; follow-up phase – all patients had absence of erythema in all groups. Resolution of vesicles: 40-45.5% of all patients had vesicles at baseline and all resolved

by end of treatment and follow-up phases. Resolution of desquamation: 70-100% of patients had desquamation at baseline (55-77.3% of cases were moderate to severe). At the end of the treatment phase; 100% of sertaconazole group had resolved compared to 90.9% in the terbinafine group and 95% in the luliconazole group. All patients had an absence of desquamation at the end of the follow-up phase. Mycological assessment showed all patients had positive KOH test for dermatophytes at baseline; however, at the end of treatment/follow-up phases, all patients had negative mycological assessments. Secondary composite scores at baseline were 6.80 in the sertaconazole group, 6.73 in the terbinafine group, and 7.05 in the luliconazole group. By the end of the treatment phase, the reductions were 97.1% in the sertaconazole group versus 91.2% (terbinafine) and 92.9% (luliconazole). At the end of follow-up, the mean total composite score was 0 for sertaconazole and luliconazole versus 0.05 in the terbinafine group. All 3 drugs were well tolerated with only one patient in the sertaconazole group withdrawing due to adverse effects (allergic contact dermatitis).

Limitations: Baseline characteristics were not statistically assessed for differences (no p-values). Statistical analysis providing p-values are not provided in the text along with results. When p-values are provided in tables, the exact number is not given but only stated as "P<0.05 vs. terbinafine." The exact numbers of adverse effects are not provided or statistically analyzed (no p-values). Power was not stated in this study thus making it uncertain if sample size was adequate. Patients with *tinea pedis* were excluded from this study. This is a common indication for luliconazole and terbinafine both. As such, this decision to exclude these patients limits the extrapolation of this data to treatment of this type of infection. While there were a similar number of women in each treatment group, overall the number of women in the study is almost one-half the number of men enrolled. This, too, can limit extrapolation. It is unclear if adherence was measured in this study as it is not mentioned.

Conclusions: The authors conclude that luliconazole is similar to terbinafine and sertaconazole in terms of mycological cure, safety profile, and overall efficacy. While the study does seem to present data that supports this claim, there is a distinct lack of statistically significant findings that may hint at the need for larger sample sizes to detect if there is a true treatment difference between these drugs. More studies of a head-to-head nature are needed to determine if luliconazole is indeed just as good as these other medications (one of which is over-the-counter) or could be a superior option.

Contraindications:

History of azole antifungal hypersensitivity[2]

None [1, 3, 4]

Precautions[2]:

Ocular Exposure: Do not administer luliconazole by ophthalmic administration. If exposure occurs, immediately flush the affected eye with cool, clean water.

Adverse Effects[1,2,3]:

No adverse effects with a incidence of >1% have been reported

Dermatologic

Application site reaction, mild (<1%)

Contact Dermatitis (Post-marketing; incidence not stated)

Cellulitis (Post-marketing; incidence not stated)

Drug Interactions:

Induction of CYP2C19 [1,4]

Based on in vitro assessment, luliconazole at therapeutics doses, particularly when applied to patients with moderate to severe *tinea cruris*, may inhibit the activity of CYP2C19; however no in vivo drug interaction trials have been conducted to evaluate the effect of luliconazole on drugs that are substrates of CYP2C19.

Induction of CYP3A4 [1,4]

Based on in vitro assessment, luliconazole at therapeutics doses, particularly when applied to patients with moderate to severe *tinea cruris*, may inhibit the activity of CYP3A4; however no in vivo drug interaction trials have been conducted to evaluate the effect of luliconazole on drugs that are substrates of CYP3A4.

Saccharomyces boulardii[4]

Antifungal agents may diminish the therapeutics effect of *Saccharomyces boulardii*

Dosing/Administration[1,2,3]:

Adult Dosing [1,2 ,3]

Interdigital *tinea pedis*: Apply a "thin layer" of cream to affected area and approximately 1 inch of the immediate surrounding area(s) once daily for 2 weeks

Tinea cruris or *tinea corporis*: Apply to affected area and approximately 1 inch of surrounding area(s) once daily for 1 week

Pediatrics [1,2,3]

Safety and efficacy have not been established in children <18 years of age; therefore no dosing recommendations exist

Elderly [1,2]

No special dosing recommendations exist as no overall differences in safety or effectiveness have been observed; however, the greater sensitivity of some elderly cannot be ruled out

Renal Impairment [2]

No dosage adjustments are necessary

Hepatic Impairment [2]

No dosage adjustments are necessary

Use in special circumstances[1]:

Pregnancy

Luliconazole is pregnancy category C as no adequate or well-controlled studies have evaluated its use in pregnant women. Luliconazole should only be used in this population if the benefits outweigh the risks. Animal studies exist with pregnant rabbits and rats. While no teratogenicity occurred in rabbits, increased mortality was noted in rat fetuses when subcutaneous doses of luliconazole equivalent to 3 times the maximum recommended human dose (MRHD) were used during organogenesis.

Lactation

It is currently unknown if luliconazole is excreted into human milk. Caution should be used when administering luliconazole to women who are breastfeeding.

Conclusion:

Literature presents luliconazole as an effective agent for treating fungal infections (such as *tinea pedis*) that eradicates offending fungi with minimal adverse effects; however, poor study design and overall lack of convincing comparative head-to-head studies make it questionable if luliconazole is better than its competitors. More studies of higher caliber need to be completed to determine luliconazole's place in therapy. As an agent whose exact arrival on the market is unknown[4], it currently seems that luliconazole may best be reserved as a second or third line agent for treatment of its indicated infections. What will surely be higher cost due to its brand-only nature combined with a barrier to acquisition via physician visits make this medication a much more expensive alternative than OTC equivalents that have already been proven effective. This drug should be considered; however, for individuals with adherence issues due to its shorter required treatment duration of 2 weeks versus 4 weeks with many other agents. Overall, it appears that luliconazole is another weapon in the physician's armamentarium in the fight against fungal infections; however, given its cost combined with inability to prove itself more effective than its counterparts, luliconazole is a niche product that will most likely find minimal use versus over-the-counter and easier-to-obtain medications.

Recommended References:

1. Luzu [package insert]. Bridgewater, NJ: Medicis. 2013.
2. Luliconazole. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: http://www.clinicalpharmacology.com Accessed: January 13, 2014.
3. Luliconazole. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: January 13, 2014.
4. Luliconazole. Lexi-Drug [database online]. Lexi-Comp, Inc; January 13, 2014.

5. Luliconazole Topical. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: January 13, 2014.
6. Jones T, Tavakkol A. Safety and tolerability of luliconazole solution 10-percent in patients with moderate to severe distal subungual onychomycosis. Antimicrob Agents Chemother. 2013; 57(6); 2684-9,
7. Watanabe S, Takahashi H, Nishikawa T. Dose-finding comparative study of 2 weeks of luliconazole cream treatment for tinea pedis – comparison between three groups (1%, 0.5%, 0.1%) by a multi-center randomized double-blind study. Mycoses. 2007; 50(1). 35-40.
8. Watanabe S, Takahashi H, Nishikawa T, et al. A comparative clinical study between 2 weeks of luliconazole 1% cream treatment and 4 weeks of bifonazole 1% cream treatment for tinea pedis. Mycoses. 2006; 49(3): 236-41.
9. Jerajani HR, Janaki C, Kumar S, et al. Comparative assessment of the efficacy and safety of sertaconazole (2%) cream versus terbinafine cream (1%) versus luliconazole (1%) cream in patients with dermatophytoses: a pilot study. Indian J Dermatol. 2013; 58(1). 34-8.

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