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## LULICONAZOLE: A NEW DRUG FOR SKIN INFECTION

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### ABSTRACT

*Luliconazole is an imidazole antifungal agent with a unique structure, as the imidazole moiety is incorporated into the ketene dithioacetate structure. Luzu (luliconazole) Cream, 1% is an azole antifungal product indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms Tricophyton rubrum and Epidermophyton floccosum in patients 18 years of age and older. For interdigital tinea pedis, luliconazole is applied once daily for two weeks; for tinea cruris and tinea corporis, luliconazole is applied once daily for one week. (one week for tinea corporis/cruris and 2 weeks for tinea pedis). This product was first developed and approved for use in Japan and has been marketed there since 2005. The drug product formulation was not changed for the US clinical development program or for the proposed US commercial drug product except for the grade of excipients. Luliconazole is a new molecular entity. Imidazole antifungal that alters the fungal cell membrane; interacts with 14-alpha demethylase (an enzyme necessary for conversion of lanosterol to ergosterol), inhibiting the synthesis of ergosterol which is an essential component of the membrane; increases cell permeability causing leakage of cellular contents*

### Introduction:

Luliconazole is an imidazole antifungal agent that has been shown to have potent activity against a variety of fungi, especially dermatophytes. This evidence-based review details the pharmacodynamics of topical luliconazole and outlines its place in the treatment of fungal infections. The English language medical literature was searched in October 2013 using the search terms “luliconazole” A total of 17 publications was identified using the above search strategy. These included six clinical trials, ten preclinical studies, and one Phase I–II pharmacokinetic study. The search was repeated in March 2014, yielding one more clinical trial. Three meeting abstracts were also included.

### Luliconazole 1% cream:

The pharmacokinetics of luliconazole 1% cream were investigated in 12 participants with moderate to severe tinea pedis and eight participants with moderate to severe tinea cruris. The participants applied luliconazole 1% cream once daily for 15 days. Luliconazole plasma concentrations were measurable in all participants on day 15 and varied little within the 24-hour interval. The mean  $\pm$  standard deviation of the maximum concentration ( $C_{max}$ ) was  $0.40 \pm 0.76$  ng/mL and  $4.91 \pm 2.51$  ng/mL after the first dose, and  $0.93 \pm 1.23$  ng/mL and  $7.36 \pm 2.66$  ng/mL after the final dose in the participants with tinea pedis and tinea cruris, respectively. The mean time to reach  $C_{max}$  ( $T_{max}$ ) was  $16.9 \pm 9.39$  hours after the first dose and  $5.8 \pm 7.61$  hours after the final dose for the participants with tinea pedis, and was  $21.0 \pm 5.55$  hours after the first dose and  $6.5 \pm 8.25$  hours after the final dose in the participants with tinea cruris. In participants with tinea pedis, exposure to luliconazole as expressed by area under the concentration time curve ( $AUC_{0-24}$ ) was  $6.88 \pm 14.50$  ng\*hr/mL after the first dose and  $18.74 \pm 27.05$  ng\*hr/mL after the final dose. Exposure to luliconazole, as expressed by  $AUC_{0-24}$  was

85.1±43.69 ng\*hr/mL after the first dose and 121.74±53.36 ng\*hr/mL after the final dose in the participants with tinea cruris.



The antifungal activity of luliconazole has been compared to that of other commercially available agents in vitro. The minimum inhibitory concentration for luliconazole was 2–4 times lower than lanconazole and almost equal to or marginally lower than terbinafine for *T. rubrum* and *T. mentagrophytes* strains. Luliconazole was shown to have the highest antifungal activity against *Trichophyton spp.* of currently available topical antifungal drugs and was also highly effective against *Candida*. Luliconazole 1% was also found to successfully eradicate experimentally-induced *T. mentagrophytes* infections in half the time or less required for 1% terbinafine cream and bifonazole 1% cream. Promising findings from preliminary studies lead to the clinical investigation of luliconazole's efficacy in treating tinea pedis, tinea cruris, and tinea corporis infections.

#### Regulatory History:

A Pre-IND meeting was held on January 16, 2007 with Janus Pharmaceuticals, Inc. (with Catalyst Pharmaceutical Research, LLC as the US regulatory agent). Original IND 76049 to support clinical development of luliconazole for the treatment of interdigital tinea pedis was submitted on August 24, 2007, and received on August 27, 2007. On November 21, 2008, the US regulatory agent for the IND changed to Topica Pharmaceuticals, Inc. An End-of-Phase 2 meeting regarding the interdigital tinea pedis indication was held on December 16, 2009, and was followed by submission of a Special Protocol Assessment (SPA) request on May 21, 2010 for review of the protocol that would support two identically designed trials in subjects with interdigital tinea pedis. An SPA Agreement letter was issued on July 7, 2010. On September 15, 2010, the IND was transferred to Medicis Pharmaceutical Corporation.

#### Disease Overview:

Fungal infections are a major health problem and an important cause of morbidity.<sup>1</sup> Fungal infections may be categorized as superficial or invasive. Superficial fungal infections affect as many as 20%–25% of the world's population and are associated with interference with daily activities, poor quality of life, and health care expenditure.<sup>1</sup> Invasive fungal infections are usually encountered in the presence of one or more predisposing factors, such as in critically ill or immunocompromised patients and those with indwelling catheters and devices, and deep or systemic fungal infections are an important cause of hospitalization and mortality.

Superficial fungal infections can be attributed to dermatophytes, *Candida*, and *Malassezia spp.* infection. Dermatophytes are aerobic fungi and the most common offenders in superficial fungal infections.

Physiologically, these dermatophytes have the ability to digest keratin for growth and replicate in the superficial layers of the epidermis. Consequently, in clinical practice, the body parts most affected by dermatophytic infection are those rich in keratin, such as the hair, skin, and nails. Survival of embedded arthroconidia for years in scales of hair and skin leads to frequent recurrence or relapse. The causative dermatophytes belong to three genera, ie, *Trichophyton*, *Microsporum*, and *Epidermophyton*. The classic presentation of dermatophytosis is that of an annular or ring-shaped red scaly plaque with central clearing, often associated with severe pruritus. The clinical manifestations of dermatophyte infections vary according to the site of infection and the patient's immunologic response. Genetic susceptibility is also known to affect the predisposition to dermatophyte infections.<sup>2</sup> Tinea pedis, or dermatophytosis of the feet, is the commonest presentation, and is most frequently caused by *Trichophyton rubrum*. Tinea cruris and tinea corporis are the next most common fungal infections, and are caused by *T. rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. Onychomycosis, or invasion of the nail plate by fungi, can be due to dermatophytes, *Candida*, or non-dermatophytic molds.

Candidosis is an infection caused by yeasts of the genus *Candida*. Superficial infections of the mucous membranes and skin are most frequent, but *Candida* can also cause deep invasive disease, including septicemia, endocarditis, and meningitis. *Candida albicans* is the member of the genus most commonly isolated from cutaneous infections, while others such as *C. tropicalis*, *C. pseudotropicalis*, *C. parapsilosis*, and *C. krusei* are occasional causes of human infection, seen more commonly in disseminated infections and in immunocompromised hosts. Oral candidiasis, or oral thrush, is an infection of the oral mucosa with the yeast. Most cases of cutaneous candidosis occur in the skin folds or where occlusion by clothing or medical dressings produces abnormally moist conditions. Periorificial areas and fingers that are frequently contaminated with saliva are also at risk



#### **Pharmacology:**

#### **Mechanism of Action:**

Imidazole antifungal that alters the fungal cell membrane; interacts with 14-alpha demethylase (an enzyme necessary for conversion of lanosterol to ergosterol), inhibiting the synthesis of ergosterol which is an essential component of the membrane; increases cell permeability causing leakage of cellular contents

#### **Absorption:**

#### **Tinea pedis**

- Peak plasma concentration: 0.4 ng/mL (first dose); 0.93 ng/mL (final dose)
- Peak plasma time: 16.9 hr (first dose); 5.8 hr (final dose)

- AUC: 6.88 ng•hr/mL (first dose); 18.74 ng•hr/mL (final dose)

#### **Tinea cruris**

- Peak plasma time: 21 hr (first dose); 6.5 hr (final dose)
- Peak plasma concentration: 4.91 ng/mL (first dose); 7.36 ng/mL (final dose)
- AUC: 85.1 ng•hr/mL (first dose); 121.74 ng•hr/mL (final dose)

#### **Clinical Features:**

##### **1. Distal and Lateral Subungual Onychomycosis**

Fungi reach the nail through the hyponychium and invade the undersurface of the nail unit plate spreading proximally. Distal and lateral subungual onychomycosis (DLSO) usually affects one or both of the great toenails and is also usually associated with tinea pedis . The nail plate appears yellow-white, is detached due to onycholysis, with distal subungual hyperkeratosis . Less frequently, a brown, black or orange discoloration of the onycholytic nail can be seen . A possible presentation of DLSO due to dermatophytes is dermatophytoma, a subungual accumulation of hyphae and scales, scarcely reached by antifungals, which require excision of the area and systemic treatment. DLSO may be associated with black pigmentation of the nail (“fungal melanonychia”) , when the pathogen is the Melanoides variant of *Trichophyton rubrum* or other fungi that produce melanin, like *Neoscytalidium dimidiatum* or *Aspergillus niger* . Onychomycosis due to non-dermatophytes is typically associated with a marked periungual inflammation . Differential diagnoses of DLSO include traumatic onycholysis (usually symmetrical and subungual hyperkeratosis is absent) and nail psoriasis (diffuse hyperkeratosis, several/all toenail involved, others skin and nail signs of psoriasis).

##### **2. White Superficial Onychomycosis**

Fungi invade the dorsal nail plate and form colonies that appear as white opaque formations, easily scraped away. The classical form is due to *Trichophyton interdigitale*, where dermatophytes colonize the most superficial layers of the nail plate without penetrating it , but *Fusarium* spp. and other molds may cause a white superficial onychomycosis (WSO) with a deeper nail invasion. Tinea pedis interdigitalis (athlete’s foot) due to *T. interdigitale* is common . Differential diagnosis includes superficial nail fragility due to prolonged wearing of nail polish and transverse toenail leukonychia due to trauma.

##### **3. Proximal Subungual Onychomycosis**

Fungal elements are typically located in the ventral nail plate, producing a proximal leukonychia. Proximal subungual onychomycosis (PSO) due to dermatophytes is very rare, and in the past, the form due to *T. rubrum* was considered as a sign of HIV infection. It presents as a white area under the proximal nail plate, in the lunula area . PSO is a common presentation of non-dermatophyte mold infection, especially due to *Aspergillus* sp. and *Fusarium* sp., and acute periungual inflammation is often associated. Differential diagnosis includes acute bacterial paronychia and pustular psoriasis of the nail.

##### **4. Endonyx Onychomycosis**

Endonyx onychomycosis is characterized by massive nail plate invasion in the absence of nail bed involvement. Clinically, the affected nail may show lamellar splitting and a milky white discoloration. The nail plate is firmly attached to the nail bed, and there is no nail bed hyperkeratosis or onycholysis . This type of infection is very rare and caused by *T. soudanense* or *T. violaceum*.

##### **5. Total Dystrophic Onychomycosis**

Total dystrophic onychomycosis (TDO) is the most severe stage of onychomycosis, and it can result from a long-standing DLSO or PSO. The nail plate is diffusely thickened, friable and yellowish color.



### Newer topical antifungals:

Luliconazole, an azole antifungal has fungicidal action against *Trichophyton* species similar to or more than that of terbinafine. Available in 1% cream formulation, it is effective as once daily application for 1–2 weeks for dermatophytic infection. Approved by the US Food and Drug Administration for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis, it has a favorable safety profile. Econazole nitrate foam preparation has also shown its efficacy over foam vehicle for tinea pedis. However, these newer drugs are costlier which in turn may lead to issues of adherence to treatment in resource-poor settings, and may predispose to development of resistance.

### Side Effect:

- Luliconazole topical is an antifungal medication that fights infections caused by fungus.
- Luliconazole topical (for the skin) is used to treat athlete's foot (tinea pedis) or jock itch (tinea cruris) in adults and children who are at least 12 years old.
- This medicine is also used to treat ringworm (tinea corporis) in adults and children at least 2 years old.
- Luliconazole topical may also be used for purposes not listed in this medication guide.
- Follow all directions on your medicine label and package. Tell each of your healthcare providers about all your medical conditions, allergies, and all medicines you use.
- You should not use luliconazole topical if you are allergic to it.
- It is not known whether this medicine will harm an unborn baby. Tell your doctor if you are pregnant or plan to become pregnant.
- It may not be safe to breast-feed a baby while you are using this medicine. Ask your doctor about any risks.
- Luliconazole topical is not approved for use by anyone younger than 18 years old.

### Conclusion:

Luliconazole is a novel broad-spectrum imidazole antifungal. Its antifungal ability has also been shown to surpass its commercial counterparts in vitro. The results from Phase III vehicle-controlled studies showed that luliconazole 1% was significantly more effective than vehicle in rapidly resolving the signs and symptoms of tinea pedis and tinea cruris, in addition to successfully eradicating the underlying fungal infection. When luliconazole 1% was evaluated against bifonazole 1% for tinea pedis, no significant difference in the rate of overall cure, resolution of symptoms, or conversion to negative mycology between agents was found, demonstrating that short-duration treatment for 2 weeks with luliconazole was as effective at curing tinea pedis as 4 weeks' treatment with bifonazole.

Two studies compared luliconazole 1% cream to sertaconazole cream among other topical agents. Both studies found that participants treated with sertaconazole had higher rates of resolution of clinical signs and symptoms compared to luliconazole; yet the results of these studies are questionable due to defects with study

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design and unclear study conduct and ambiguous reporting. The comparative effectiveness and safety of luliconazole and sertaconazole remains unclear and well-designed head-to-head trials of newer antifungals are warranted to establish these agents' relative efficacy in treating tinea infections.

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