Cross-Discipline Team Leader Review

Date	January 26, 2018
From	David Kettl, MD, FAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 204153 Supplement 005
Applicant	Medicis/Valeant Pharmaceuticals
Date of Submission	February 27, 2017
PDUFA Goal Date	April 21, 2018
Proprietary Name	Luliconazole
Established or Proper Name	Luzu
Dosage Form(s)	Topical Cream, 1%
Applicant Proposed Indication(s)/Population(s)	Interdigital tinea pedis, tinea cruris, and tinea corporis; 2 years of age and older
Applicant Proposed Dosing Regimen(s)	Apply topically onto affected areas plus a ½ inch margin of healthy surrounding skin once-daily for 2 weeks in treatment of interdigital tinea pedis, and once-daily for 1 week in the treatment of tinea cruris and tinea corporis due to *Trichophyton rubrum* and *Epidermophyton floccosum* in children ≥ 2 years of age and older.
Recommendation on Regulatory Action	***Approval***
Recommended Indication(s)/Population(s) (if applicable)	LUZU (luliconazole) Cream, 1% is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms Trichophyton rubrum and Epidermophyton floccosum.
Recommended Dosing Regimen(s) (if applicable)	Once daily for one-two weeks

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Luliconazole is available in the United States under NDA 204153 as LUZU approved November 14, 2013 for the 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. The safety and efficacy of luliconazole cream, 1% was previously demonstrated in the original application approved for treatment of adults with tinea pedis, tinea cruris, and tinea corporis.

The 2013 approval letter included PREA PMR's for evaluation of pharmacokinetics in tinea pedis and cruris, and to evaluate safety and efficacy for tinea corporis, which historically was included for products which had demonstrated safety and efficacy for tinea pedis and cruris.

A single PK study was used to evaluate the safety of luliconazole cream, 1% in the treatment of tinea pedis and tinea cruris in subjects 12 to 17 years of age (inclusive) in order to fulfill a PREA post marketing requirement. The study was conducted appropriately and is adequate to fulfill the PREA PMR and provide support to update the existing labeling for pediatric populations with tinea pedis and cruris, which are principally comprised of adolescents as tinea cruris and tinea pedis are both very uncommon in pre-pubertal children. No additional studies are recommended.

A separate supplement (004) was submitted to address the PREA PMR for tinea corporis. Both PREA PMR's have been adequately addressed to support labeling in pediatric patients and both supplements 004 and 005 are recommended for approval. Labeling to address information contained in both supplements is being communicated to the applicant in a single document.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Tinea pedis is a fungal infection of the foot and is usually caused by dermatophytes, aerobic fungi that produce keratinase, an enzyme that breaks down in the stratum corneum of the skin. The vast majority of tinea pedis cases are caused by T. rubrum, E. floccosum or T. mentagrophytes. • The clinical manifestations of tinea pedis usually present as a pruritic, erythematous, inflamed region most often seen	The efficacy of luliconazole cream, 1% was previously demonstrated in the original application approved for treatment of adults with tinea pedis, tinea cruris, and tinea corporis. Multiple antifungal treatments, both by prescription, and over the counter are available for these conditions, and are summarized in the table

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	between the toes (interdigital type) or a more severe, prolonged form that may involve the entire bottom and lateral aspects of the foot (moccasin type) or sometimes located on the sole (vesicular type). • Diagnosis of tinea pedis is usually by physical examination, in combination with laboratory evidence of the fungal organisms by direct microscopic examination with potassium hydroxide (KOH) followed by culture for dermatophytes. • Tinea cruris involves fungal infection of the groin and adjacent skin. It is the second most common clinical presentation caused by dermatophytes. The upper, inner thighs are affected and sometimes erythema extends to the groin and the pubic area. The most common organisms associated with this disease are T. rubrum and E. floccosum, with less commonly T. mentagrophytes involved. Tinea corporis involves fungal infection of the arms and legs, especially on glabrous skin; however, it may occur on any part of the body.	below.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Luliconazole is available in the United States under NDA 204153 as LUZU approved November 14, 2013 for the 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. • Luliconazole Cream, 1% was approved on April 11, 2005 in Japan under the trade names Lulicon® Cream, 1% and Lulicon® Solution, 1%.	**Topical Antifungal Agents (Tinea Pedis)** Econazole (Spectazole) Ciclopirox (Loprox) Sulconazole (Exelderm) Naftifine (Naftin) 1% Naftifine (Naftin) 2% Gel Oxiconazole (Oxistat) Clotrimazole (Lotrimin AF) Terbinafine (Lamisil Cream) Butenafine (Mentax)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Terbinafine (Lamisil Solution) Butenafine (Lotrimin Ultra) Sertaconazole (Ertaczo)
Benefit	This was an open-label pharmacokinetics study conducted at two investigational sites to determine the pharmacokinetics of luliconazole cream 1% in adolescent subjects (age 12 to <18 years) with either moderate to severe interdigital tinea pedis on both feet or moderate to severe tinea cruris. Formal statistical testing was not proposed or evaluated. Efficacy was not formally evaluated.	Luliconazole is available in the United States under NDA 204153 as LUZU approved November 14, 2013 for the 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. A single PK study was used to evaluate the safety of luliconazole cream, 1% in the treatment of tinea pedis and tinea cruris in subjects 12 to 17 years of age (inclusive) in order to fulfill a PREA post marketing requirement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Safety was evaluated in all subjects who received at least one application of study drug (the safety population). There were 30 subjects in the safety population (15 subjects in the tinea pedis group and 15 subjects in the tinea cruris group).	A total of 3 AEs were reported in 3 subjects in the tinea pedis group and 1 AE was reported in 1 subject in the tinea cruris group. Treatment-emergent AEs were reported by 2 subjects in the tinea pedis group and 1 subject in the tinea cruris group. There were no serious adverse events reported. There were no subjects discontinued from the study as a result of an adverse event. No significant safety events were observed. Labeling is adequate for communication of risk, and specific risk management programs are not recommended for this product.

2. Background

Luliconazole Cream, 1% was approved on November 14, 2013 for the topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by organisms Trichophyton rubrum and Epidermophyton floccosum in subjects 18 years of age and older.

Historically, once safety and efficacy for tinea pedis and tinea cruris was demonstrated, efficacy in tinea corporis was assumed due to similarities in the causative organisms among these topical fungal infections. Since the advent of PREA, studies demonstrating the safety and efficacy for topical antifungals are now recommended for the indication of tinea corporis in the absence of other safety information. Tinea corporis occurs in younger children, while tinea pedis and cruris are uncommon in pre-pubertal children.

This was discussed with the Pediatric Review Committee. The Committee agreed with the review team recommendations that a deferral to conduct studies in pediatric subjects 12-18 years in tinea cruris and pediatric subjects 2 years of age and older in tinea corporis be granted and that the following PMR's be attached to the NDA approval:

- Maximum use PK safety study in pediatric subjects ≥ 12 years to 17 years, 11 months of age in all indications is recommended.
- Conduct of a multicenter, randomized, blinded, vehicle-controlled study with use of luliconazole cream, 1% for the treatment of tinea corporis in pediatric patients ≥ 2 years of age as a PREA PMR.

The approval letter lists the PMR's as follows:

2101-1 Conduct a multi-center, randomized, blinded, vehicle-controlled study, including pharmacokinetic assessments, with luliconazole cream 1% for the treatment of tinea corporis in pediatric patients 2 years of age and older.

Final Protocol Submission:	01/2014
Study Completion:	11/2016
Final Report Submission:	04/2017

2101-2 Conduct a maximum use pharmacokinetic safety study in pediatric patients 12 years to 17 years 11 months of age with interdigital tinea pedis and tinea cruris.

Final Protocol Submission:	01/2014
Study Completion:	10/2016
Final Report Submission:	02/2017

This supplement includes the final study report of the aforementioned PMR for an open-label study to assess the pharmacokinetics (PK) of luliconazole Cream 1% in pediatric patients with moderate to severe interdigital tinea pedis or tinea cruris under maximal use conditions.

A separate supplement (004) provides the study report for tinea corporis pediatric trial. These supplements are reviewed in tandem and labeling to address both PREA PMR's will be conveyed to the applicant in a single draft document, with anticipated action on both supplements simultaneously.

3. Product Quality

LUZU (luliconazole) Cream, 1% is a white cream and is supplied in 30 g and 60 g tubes.

The applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product in the original NDA application. No new CMC information is provided in this supplement. There are no outstanding issues from a chemistry perspective for this supplement.

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety profile for luliconazole cream is supported by nonclinical studies reviewed under the original NDA. No new nonclinical information was included in this supplement. There are no outstanding issues from a nonclinical perspective for this supplement.

5. Clinical Pharmacology

Pharmacokinetic (PK) assessment was performed in approximately 15 subjects (12 active + 3 vehicle) at selected sites for each indication (tinea pedis and tinea cruris). Approximately 3 g of Luliconazole cream was administered once daily in the morning for 15 days in subjects with tinea pedis and once daily in the morning for 8 days in subjects with tinea cruris. In subjects with tinea pedis the drug was applied to the top surface of both feet up to the ankles and in subjects with tinea cruris the drug was applied on the groin, thigh and abdomen area.

Comparing the systemic exposure for tinea pedis on Day 15 between adolescent and adults, the Cmax and AUC0-24 in adolescent subjects were approximately 3.5 and 3.2 fold higher, respectively compared to adults.

Comparing the systemic exposure for tinea cruris on Day 8 between adolescent and adults, the Cmax and AUC0-24 in adolescent subjects were approximately 2.7 and 2.5 fold higher, respectively compared to adults.

Dr. Chinmay Shukla, the clinical pharmacology reviewer, noted that the applicant was asked to conduct the maximal use PK trial in subjects with both tinea pedis and tinea cruris occurring in the same subject. However, the applicant conducted the study in subjects having the two diseases separately. Comparing the PK data, the Cmax and AUC0-24 on Day 8 in subjects with tinea cruris was approximately 3.9 fold and 4.1 fold higher, respectively, compared to subjects with tinea pedis. Hence the overall contribution of tinea pedis to systemic exposure in subjects with both conditions would be expected to result in levels that would be essentially unchanged versus tinea cruris alone given the observed variability and as there are no systemic safety concerns with this product, the current study design is considered acceptable.

Dr. Shukla concludes in his review that the observed systemic concentrations of luliconazole in this study in subjects with tinea corporis is lower than in subjects with tinea cruris. Results of in vitro studies indicated that therapeutic doses of LUZU Cream, 1% did not induce CYP1A2, 2B6, and 3A4. Hence there appears to be no additional concerns of drug interaction potential in this new population.

However, Dr. Shukla concluded that the labeling should indicate that in subjects with tinea cruris, luliconazole systemic concentrations suggests that it could be a moderate inhibitor of CYP2C19 in this population. Labeling addressing these issues has been added to section 12.3 and forwarded to the applicant for concurrence.

From a Clinical Pharmacology standpoint, this application was deemed acceptable for an approval action pending final agreement on labeling. The PMR has been deemed adequately addressed.

6. Clinical Microbiology

No information related to clinical microbiology was included in this supplement.

7. Clinical/Statistical- Efficacy

This was an open-label pharmacokinetics study conducted at two investigational sites to determine the pharmacokinetics of luliconazole cream 1% in adolescent subjects (age 12 to <18 years) with either moderate to severe interdigital tinea pedis on both feet or moderate to severe tinea cruris. Formal statistical testing was not proposed and none was provided in the supplement. The PMR study protocol specified that there would be no hypothesis testing for efficacy. Other than changes related to the pediatric age groups in labeling, no changes to section 14 of labeling are recommended.

8. Safety

This clinical trial included assessments of AE at all visits. Safety laboratory assessments (hematology, chemistry, and urinalysis) were completed at Baseline and end-of-treatment. A urine pregnancy test at Screening, Baseline, end-of-treatment, and end-of-study was completed.

A total of 3 AEs were reported in 3 subjects in the tinea pedis group and 1 AE was reported in 1 subject in the tinea cruris group. Treatment-emergent AEs were reported by 2 subjects in the tinea pedis group and 1 subject in the tinea cruris group. There were no deaths or serious adverse events reported. There were no subjects discontinued from the study because of an adverse event.

One non-treatment emergent AE was reported during the study. Subject (101028) in the tinea pedis group had an AE (headache) that occurred on study Day -7, prior to the application of any study treatment. This event was considered mild in intensity and not related to study treatment. The headache was treated with concomitant medication and resolved on Day 7.

Clinical laboratory evaluations showed no mean changes in laboratory parameters over time, no shift in percentages of subjects who had normal values at Baseline and abnormal values at the end-of treatment, and no individually significant laboratory results reported as AEs were indicative of safety signal or indicated a clinically meaningful difference between luliconazole cream, 1% and vehicle cream.

No new safety information related to adverse events observed in this trial are recommended for labeling.

9. Advisory Committee Meeting

This supplement for this azole antifungal presented no novel or complex regulatory issues that required the input of the DODAC advisory committee.

10. Pediatrics

The PREA PMR should be considered fulfilled by this supplement. Labeling changes addressing the relevant age groups are included in the draft labeling conveyed to the applicant.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application. No clinical study sites were recommended for inspection due to the limited nature of the study.

This submission was originally submitted on 02/27/2017. However, the review clock did not start until 06/14/2017 due to delay in payment of PDUFA user fees.

There are no other outstanding regulatory issues.

12. Labeling

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trial for the sNDA as well as DMEPA, DRISK, and DDMAC consultative reviews.

Labeling is adequate to communicate necessary safety information to prescribers. The primary changes to the currently approved labeling reside in Section 12.3.

This supplement is reviewed in tandem with supplement 004, the PREA PMR trial for tinea corporis. Labeling changes related to both supplements will be conveyed in the same draft document. Applicant agreement with Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review, but there are no other outstanding issues related to labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

REMS is neither required nor recommended for this topical antifungal product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The completed study fulfilled the Post Marketing Requirements (PMR) 2101-1.

No additional PMR/PMC's are recommended by the review team for this supplement.

14. Recommended Comments to the Applicant

A regulatory letter may be sent to the applicant acknowledging that the completed study fulfilled the Post Marketing Requirements (PMR) 2101-2.

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/s/

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01/26/2018