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 004
Applicant	Medicis/Valeant Pharmaceuticals
Date of Submission	April 21, 2017
PDUFA Goal Date	February 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 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.

This Supplement (004) was submitted to address the PREA PMR for tinea corporis and includes the study report for the safety, efficacy, and PK data for pediatric tinea corporis.

In a separate supplement 005, 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.

Both PREA PMR's have been adequately addressed to support labeling in pediatric patients and both supplements 004 and 005 are recommended for approval. No significant safety signals have been identified in these studies. Labeling to address information contained in both supplements is being communicated to the applicant in a single document which includes the relevant information for the pediatric age groups.

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 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The clinical manifestations of tinea pedis usually present as a pruritic, erythematous, inflamed region most often seen 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.	Multiple antifungal treatments, both by prescription, and over the counter are available for these conditions, and are summarized in the table 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	The applicant provided the results for their Post Marketing Requirement (PMR) study in 75 pediatric subjects. The primary objective of the study was to evaluate the safety and efficacy of Luzu cream, 1% when applied topically for 7 days in pediatric subjects (2-17 years of age, inclusive) with tinea corporis. The same efficacy endpoints that were evaluated in the adult trials were evaluated in this PMR study as well, but the PMR study protocol specified that there would be no hypothesis testing for efficacy.	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 treatment effect for complete clearance was 71% versus 36% for vehicle, and the results of this trial are recommended for labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	18 adverse events (AEs) were reported in 9 subjects in the Luzu cream, 1%, and a total of 2 AEs were reported in 2 vehicle subjects. The applicant reported that they were all treatment-emergent AEs. There were no SAEs. There were no AEs leading to withdrawal of the subject from the study. The most frequently reported TEAE was nasopharyngitis, reported in 4 subjects (6.7%) in the luliconazole 1% group and 2 subjects (13.3%) in the Vehicle group. Headache was reported in 3 subjects (5.0%) in the luliconazole 1% group and 0 subjects in the Vehicle group. None of the TEAEs were severe, but 2 of the TEAEs reported in the luliconazole 1% group, one case of nasopharyngitis and one case of headache were of moderate severity. None of the TEAEs were related to treatment.	Safety experience for this trial will be included in labeling, but no events are recommended for Warnings and Precautions. None of the adverse events are considered significant for prescribers. 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.

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 the treatment of tinea corporis in pediatric patients 2 years of age and older and labeling proposals to incorporate these findings into approved labeling.

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

This was a randomized multi-center, double-blind, vehicle controlled study evaluating the safety, efficacy and pharmacokinetics (PK) of Luliconazole cream, 1% in pediatric subjects 2 to 17 years of age with tinea corporis. Approximately 75 male and female subjects aged 2 years to 17 years with tinea cruris were randomized (4:1) to treatment with either Luliconazole Cream 1% or Vehicle Cream once daily for 7 days.

The diagnosis of tinea corporis was confirmed by the detection of fungal hyphae on a KOH wet mount test. Study drug was applied once daily in the morning for 7 days to the affected area and approximately 1 inch of the immediate surrounding area. The first and last (Day 7) administration of study medication was completed at the investigational site and rest of the applications of study medication were administered by the subjects/ caregivers at home.

Pharmacokinetic (PK) assessment was performed in approximately 15 subjects (12 active + 3 vehicle) at selected sites. Plasma levels of luliconazole and z-luliconazole (metabolite) were obtained on Day 7 within 15 minutes prior to the final dose of the drug and at approximately near the expected Tmax based on prior PK experience in adult subjects with tinea cruris (6 hours after the final dose).

The primary review issue was the lack of recorded assessments for affected and treated body surface area. Reviews were based on estimates from standardized BSA calculators.

The clinical pharmacology reviewer, Dr. Chinmay Shukla, concluded that the following PK information was adequately demonstrated and should be included in labeling:

Systemic concentrations of luliconazole were assessed at pre-dose and at 6 hours post-dose on the last day of treatment in a subset of 12 subjects 2 to 17 years of age with tinea corporis. Following once daily treatment with LUZU cream, 1% for 7 days, luliconazole systemic concentrations were quantifiable in all the 12 subjects.
The mean ± SD daily dose of LUZU Cream, 1% in these 12 subjects was 2.84 ± 1.82 g. The mean ± SD concentration of the of luliconazole at 15 minutes prior to dosing and at 6 hours post-dose on Day 7 was 4.63± 2.93 ng/mL and 4.84 ± 3.33 ng/mL, respectively.

The observed systemic concentrations of luliconazole in this study in subjects with tinea corporis are lower than in subjects with tinea cruris. Dr. Shukla concludes that there appears to be no additional concerns of drug interaction potential in this population and no labeling recommendations are recommended for the data in this supplement related to drug interactions.

From a Clinical Pharmacology standpoint, Dr. Shukla concludes that this application was deemed acceptable pending final agreement on labeling. The PMR has been adequately addressed and this can be conveyed to the applicant.

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

The primary objective of the study was to evaluate the safety and efficacy of Luzu cream, 1% when applied topically for 7 days in pediatric subjects (2-17 years of age, inclusive) with tinea corporis. The PMR study protocol specified that there would be no hypothesis testing for efficacy, and no formal statistical analysis was conducted. The protocol was reviewed in 2014 and comments regarding sample size and other aspects of the protocol were conveyed.

The same efficacy endpoints that were evaluated in the adult trials were evaluated in this PMR study as well. The endpoints were:

- Complete clearance was defined as achieving mycological cure and clinical cure which are defined below
  - Mycological Cure was defined as having both a negative KOH and negative fungal culture
  - Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus)
- Effective Treatment was defined as negative KOH and culture results and at most mild erythema and/or scaling with no pruritus

Dr. Carin Kim, the Agency Biostatistical reviewer, describes a total of 75 pediatric subjects with tinea corporis enrolled from 3 investigational sites in Latin America, and they were randomized in a 4:1 ratio to the Luzu cream, 1% or vehicle arms. Subjects were enrolled from 3 sites in Latin America (2 sites in Dominican Republic and 1 in Honduras). Study treatment was applied to the affected area and approximately one inch of the surrounding area once daily in the morning at approximately the same time for 7 days. Subjects returned to the investigational site for safety and efficacy observations at Days 7, 14, 21, and 28.

The enrolled subjects had a mean age of 8.2 and 9.1 for Luzu cream, 1% and vehicle cream, respectively. Approximately 72% of the enrolled subjects were male, and approximately 64% were black. All were of Hispanic or Latino ethnicity.

For the analysis, the applicant used the modified Intent to Treat (mITT) population defined as subjects who had a positive KOH wet mount and a positive fungal culture at baseline. Of the 75 enrolled subjects, 65 subjects were mITT subjects.

Efficacy tables from Dr. Kim's review are reproduced below.

Table 1. Efficacy results at Day 28

	Luzu 1% N=51	Vehicle N=14
Complete Clearance (1)	36 (70.6%)	5 (35.7%)
Mycological Cure (2)	41 (80.4%)	8 (57.1%)
Clinical Cure (3)	41 (80.4%)	6 (42.9%)
Effective Treatment (4)	39 (76.5%)	8 (57.1%)

Source: sponsor's table 11-3.
(1) Complete clearance was defined as achieving mycological cure and clinical cure which are defined below
(2) Mycological Cure was defined as having both a negative KOH and negative fungal culture
(3) Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus)
(4) Effective Treatment was defined as negative KOH and culture results and at most mild erythema and/or scaling with no pruritus

Dr. Kim notes that half of the subjects were less than 8 years of age, and subject exposure and demographics are adequate for fulfillment of the PREA PMR.

Table 7. Complete Clearance (1) by Subgroup for the mITT subjects

	Luzu 1% N=60	Vehicle N=15
Age		
<8 years old	20/30 (67%)	4/8 (50%)
≥8 years old	16/21 (76%)	1/6 (17%)
Sex		
Male	27/35 (77%)	4/12 (33%)
Female	9/16 (56%)	1/2 (50%)
Race		
White	15/16 (94%)	1/4 (25%)
Black	21/35 (60%)	4/10 (40%)

Source: reviewer's table;
(1) Complete clearance was defined as achieving mycological cure and clinical cure which are defined below. Mycological Cure was defined as having both a negative KOH and negative fungal culture.
Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus).

While Dr. Kim notes that this PMR study evaluated safety and efficacy, there were no hypothesis testing for efficacy. She concludes that there were no statistical issues affecting the overall findings, and the results will be recommended for Section 14, Clinical Studies, in Luzu labeling.

This CDTL review concurs with the Agency Biostatistical assessments, and concludes that the study is adequate to fulfill the PREA PMR. There are no outstanding issues related to efficacy assessments.

8. Safety

Local and systemic adverse event information were collected, and laboratory tests (chemistry, hematology, and urinalysis) were obtained. Baseline ECGs were obtained during screening to compared to the 12-lead ECG obtained at the completion of treatment (Visit 2).

Nine subjects (15.0%) in the Luliconazole 1% group reported 18 AEs and 2 subjects (13.3%) in the Vehicle group reported 2 AEs. All of these were TEAEs. There were no SAEs. There were no AEs leading to withdrawal of the subject from the study.

The most frequently reported TEAE was nasopharyngitis, reported in 4 subjects (6.7%) in the luliconazole 1% group and 2 subjects (13.3%) in the Vehicle group. Headache was reported in 3 subjects (5.0%) in the luliconazole 1% group and 0 subjects in the Vehicle group.

None of the safety events were considered serious by the clinical reviewer, Dr. Gary Chiang. The safety experience from this study will be included in product labeling, but none rise to the level of Warnings and Precautions.

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

Due to the requirements of PREA, pediatric trials for tinea corporis are necessary even though there is no substantial concern regarding safety or efficacy for this product and indication. Labeling changes addressing the relevant age groups are included in the draft labeling conveyed to the applicant. The PMR should be considered fulfilled by this supplement.

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.

Draft labeling for both supplements 004 and 005 will be combined for conveyance to the applicant, and simultaneous approval actions are anticipated following agreements on labeling.

There are no other outstanding regulatory issues.

12. Labeling

Prescribing Information

The applicant proposed to update the Indications and Usage section (Section 1) to allow treatment for subjects that are "2 years of age and older" with tinea corporis as well as the Clinical Studies section (Section 14) of the labeling with the information regarding the tinea corporis in pediatric subjects, and the safety and efficacy of Luzu cream, 1% for tinea corporis. Following current internal recommendations, the specific ages are not recommended to be included in the Indications section.

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. 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

The completed study fulfilled the Post Marketing Requirements (PMR) 2101-1. A regulatory letter may be sent to the applicant acknowledging that the completed study fulfilled the Post Marketing Requirements (PMR) 2101-1.

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/s/

DAVID L KETTL
01/26/2018