CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	204153/S-005
Priority or Standard	Standard
Submit Date(s)	27-FEB-2017
Received Date(s)	21-JUN-2017
PDUFA Goal Date	21-APR-2018
Division / Office	DDDP/ODE III
Reviewer Name(s)	Gary Chiang MD, MPH
Review Completion Date	25-JAN-2018
Established Name	Luliconazole
(Proposed) Trade Name	LUZU
Therapeutic Class	Azole antifungal
Applicant	Valeant Pharmaceutical Corp
Formulation(s)	Cream, 1%
Dosing Regimen	Topical once daily
Proposed Indication(s)	Interdigital tinea pedis, tinea cruris, and tinea corporis
Intended Population(s)	patients 12 years of age and older with tinea pedis and tinea cruris and 2 years of age and older with tinea corporis

Template Version: March 6, 2009

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Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical prospective, an approval recommendation is being made for the use of luliconazole cream, 1% applied 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 patients ≥ 2 years of age and older with tinea corporis and 12 years and older with tinea cruris and tinea pedis. This recommendation is predicated upon the applicant's acceptance of revised labeling. The applicant has completed the required pediatric assessments put forth in the approval letter for the original application.

2101-1 Conduct a maximal use pharmacokinetic (PK) trial with luliconazole cream 1% for the treatment of tinea pedis and tinea cruris in pediatric patients 12 years to less than 17 years of age.

The single pediatric pharmacokinetic trial in tinea pedis and tinea cruris provided sufficient evidence of safety in patients ≥ 12 years to 17 years and 11 months of age. 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. In addition, the applicant provided sufficient safety and efficacy evidence in Supplement 004 for tinea corporis patients down to 2 years of age.

1.2 Risk Benefit Assessment

Sufficient evidence of safety and efficacy is provided in this application to reason that the benefit of the drug product outweighs the risk associated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- None

1.4 Recommendations for Postmarket Requirements and Commitments

- None

2 Introduction and Regulatory Background

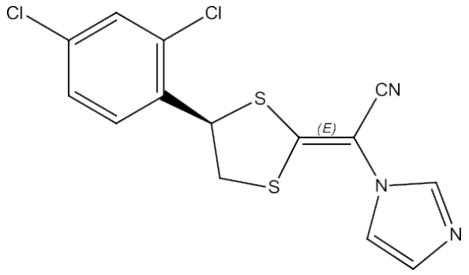
Luliconazole Cream, 1% is an imidazole antifungal with a dual mechanism of action. Luliconazole exhibits antimycotic and fungicidal activity against dermatophytes through the inhibition of ergosterol biosynthesis. In addition, luliconazole's antifungal activity includes inhibition of protease production by *Trichophyton* species.

The development plan for luliconazole cream, 1% included a Pre-IND meeting, two End-of-Phase 2 meetings, and a Pre-NDA meeting. In addition, the sponsor submitted two Special Protocol Assessments for Agency agreements. The submission includes a total of 11 U.S. clinical studies and seven clinical studies conducted in Japan to form the Japanese approval of luliconazole.

2.1 Product Information

LUZU® Cream, 1% is an imidazole antimycotic/antifungal drug with a dithiolan structure incorporated into a topical cream formulation at strength of 1% w/w. Each gram of drug product contains 10 mg luliconazole in a white cream formulation consisting of purified water, propylene glycol, methylparaben, polysorbate 60, cetostearyl alcohol, sorbitan monostearate, isopropyl myristate, medium chain triglycerides, benzyl alcohol, and butylated hydroxytoluene.

Figure 1: Molecular Structure



The product is contained in a blind-end aluminum tube with a 2, 30, or 60 gram fill volume and a (b) (4) .

The established name is luliconazole. The DMEPA approved proposed name is LUZU® (luliconazole) Cream, 1%.

Luliconazole Cream, 1% was approved on April 11, 2005 in Japan under the trade names Lulicon® Cream, 1% and Lulicon® Solution, 1%. The approved indications in Japan include the following cutaneous mycoses:

- Tinea: tinea pedis, tinea corporis, and tinea cruris
- Candidiasis: interdigital erosion and intertrigo
- Tinea versicolor

The Japanese international safety experience was considered as part of the assessment for this approval of the LUZU application.

2.2 Tables of Currently Available Treatments for Proposed Indications

It is well accepted that common tinea infections are treated with topical agents, therapeutic success is limited because of poor compliance, poor awareness regarding the disease condition by the patient, and frequent recurrence. In general, current tinea pedis therapies require once a day or twice a day treatment for up to four

weeks and current tinea cruris and tinea corporis therapies require once a day or twice a day treatment for up to two weeks, and treatment should continue for at least one week after symptoms resolved to reduce recurrence. [1]

1 Fitzpatrick, T.B., Johnson, R.A., and Wolff, K. Color Atlas and Synopsis of Clinical Dermatology. Third Edition. 1997. Section 25; pg. 3-25.

Table 1: Currently Approved Topical Antifungal Cream Formulations for Treatment of Tinea Pedis, Cruris, and Corporis

Topical Antifungal Agents (Tinea Pedis)	NDA	Dosage (Tinea Pedis)	Date of Approval	Mechanism of Action
Econazole (Spectazole)	NDA 018-751	QD for 1 month	December 23, 1982	Azole: Alters fungal cell wall membrane permeability; may interfere with RNA and protein synthesis and lipid metabolism
Ciclopirox (Loprox)	NDA 018-748	BID 4 weeks	December 30, 1982	Inhibiting transport of essential elements in the fungal cell disrupting the synthesis of DNA, RNA, and protein
Sulconazole (Exelderm)	NDA 018-738	BID 4 weeks	August 30, 1985	Substituted imidazole derivative which inhibits metabolic reactions necessary for the synthesis of ergosterol, an essential membrane component.
Naftifine (Naftin) 1%	NDA 19-599	QD for 2 weeks	February 29, 1988	Interfere with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase
Naftifine (Naftin) 2% Gel	NDA 204-286	QD for 2 weeks	June 27, 2013	Interfere with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase
Oxiconazole (Oxistat)	NDA 019-828	QD-BID 1 month	December 30, 1988	Azole: destroys membrane integrity of fungi through inhibition of ergosterol synthesis
Clotrimazole (Lotrimin AF)	NDA 020-888	BID 2-4 weeks	October 27, 1989	Azole: Binds to phospholipids in the fungal cell membrane altering cell wall permeability resulting in loss of essential intracellular elements
Terbinafine (Lamisil Cream)	NDA 020-192	Gel: BID for 7 days Cream: BID < 4 weeks	December 30, 1992	Synthetic allylamine derivative which inhibits squalene epoxidase, a key enzyme in sterol biosynthesis in fungi
Butenafine (Mentax)	NDA 020-524	BID 1 week/QD 4 weeks	October 18, 1996	Exerts fungicidal activity against dermatophytes by blocking squalene epoxidation, resulting in inhibition of ergosterol synthesis and subsequent weakening of fungal cell membrane
Terbinafine (Lamisil Solution)	NDA 020-980	BID 1 week	October 17, 1997	Synthetic allylamine derivative which inhibits squalene epoxidase, a key enzyme in sterol biosynthesis in fungi
Butenafine (Lotrimin Ultra)	NDA 021-307	BID 1 week/QD 4 weeks	December 7, 2001	Exerts fungicidal activity against dermatophytes by blocking squalene epoxidation, resulting in inhibition of ergosterol synthesis and subsequent weakening of fungal cell membrane
Sertaconazole (Ertaczo)	NDA 021-385	BID 4 weeks	December 10, 2003	Azole: alters fungal cell wall membrane permeability; inhibits the CYP-450-dependent synthesis of ergosterol

Source: Compiled by G.Chiang form DARRTS database

2.3 Availability of Proposed Active Ingredient in the United States

Luliconazole is available in the United States under the 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.

2.4 Important Safety Issues with Consideration to Related Drugs

Luliconazole cream, 1% is a synthetic imidazole drug unlike the currently marketed antifungals which are generally allylamine derivatives. As with all antifungal drug products, particular attention is directed at adverse events related to assessments of liver, kidney, cardiac parameters, and drug-drug interactions. The original application identified no serious safety concerns with luliconazole, cream 1%.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

LUZU® (luliconazole) Cream, 1% was approved on November 14, 2013. In the approval letter, the Agency specified several PMR/PMC for the applicant to complete.

- PMC 2101-5 Conduct in vitro assessments to evaluate the following:
  a) Inhibition potential of luliconazole for enzymes CYP2B6 and CYP2C8
  b) Induction potential of luliconazole for enzymes CYP1A2, CYP2B6 and CYP3A
  Further in vivo assessment to address drug interaction potential may be needed based on the results of these in vitro assessments.

  This PMC was completed and deemed fulfilled on 7-MAR-2016

- PMR 2101-3 Conduct an in vivo drug interaction trial using an appropriate probe substrate to evaluate the inhibition potential of luliconazole for CYP2C19 under maximal use conditions in subjects with tinea cruris and interdigital tinea pedis.

  This PMR was completed and deemed fulfilled on 17-MAY-2016

- PMR 2101-4 Conduct an in vivo drug interaction trial using an appropriate probe substrate to evaluate the inhibition potential of luliconazole for CYP3A4 under maximal use conditions in subjects with tinea cruris and interdigital tinea pedis. This trial may be omitted if the results from the trial with the CYP2C19 substrate (PMR 2101-3) indicate no significant interaction.

  A waiver was granted to release the sponsor from this PMR on 17-MAY-2016

- Approval of PAS updates to section 8 of the prescribing information to conform to the PLLR and proposed updates to section 12.3 to include information about CYP2C19 from a postmarketing study on 8-FEB-2017

The pediatric development plan for luliconazole included two postmarketing requirements.

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.

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.

This supplement proved for the completed PMR for 2101-2 to include labeling update for the information derived from the study.

2.6 Other Relevant Background Information

The majority of superficial fungal infections in the United States are tinea infections, which are primarily caused by three types of dermatophytes: *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. [2] The most common tinea are defined by the location of the infection as follows: tinea pedis (foot and also known as "athlete's foot"), tinea cruris (groin and surrounding issues, and also known as "jock itch"), and tinea corporis (body and commonly known as "ringworm"). These organisms are spread by human-to-human contact with infected skin scales in moist environments such as shower rooms or bathing areas. Diagnoses is usually by physical examination, in combination with laboratory evidence of the fungal organism by direct microscopic examination with potassium hydroxide (KOH) followed by culture of the dermatophyte. Tinea corporis is a superficial fungal infection of the glabrous skin (i.e., skin regions except the scalp, groin, palms, and soles) and affects persons of all age groups, but the prevalence is highest in preadolescents. [3]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The study protocol, Informed Consent Forms (ICFs), and other information for subjects were approved by the central Institutional Review Board (IRB). The IRB was (b) (4) .

3.2 Compliance with Good Clinical Practices

According to the applicant, studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, and in compliance with all International Conferences on Harmonization Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed.

2 Foster, W.K., Ghannoum M.A. and Elewski, B.E. Epideminological surveillance of cutaneous fungal infection in the United States from 1999 to 2001. *J. AM. ACAD. DERMATOL*:2004: 50 (5); 748-752.
3 Lesher, J.L. Tinea corporis. eMedicine from WebMD [Internet]. 2009 Dec [cited 2013 MAR 04].

3.3 Financial Disclosures

This study was conducted under the sponsorship of Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals, North America LLC. Clinical monitoring and statistical analyses were performed by (b) (4) .; clinical trial supplies were provided by Valeant - Bausch and Lomb CTM Supply group, Rochester, NY.

Table 2: Principle Investigators

Principal Investigator	Location (office)
Daisy Margarita Blanco Falette, MD	Instituto Dermatologico y Cirugia de Piel Calle Federico Velazquez, Esq. Albert Thomas, Ensanche Maria Auxiliadora Santo Domingo, Dominican Republic
Nelley Georgina Paz, MD	Hospital y Clinica Bendaña Ave. Circunvalacion, 3er Piso, local 312 San Pedro Sula, Honduras

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no changes to the CMC in this NDA.

4.2 Clinical Microbiology

There are no clinical microbiology safety issues in this NDA.

4.3 Preclinical Pharmacology/Toxicology

There are no Pharmacology/Toxicology safety issues in this NDA. Prior non-clinical information in the labeling is up-to-date. The minor changes in the non-clinical sections of the label have been reviewed and are deemed acceptable. Final labeling changes will be provided in the approval letter.

4.4 Clinical Pharmacology

This was an open-label PK study in adolescent subjects (aged 12 to < 18 years) in which 15 subjects with moderate to severe interdigital tinea pedis and 15 subjects with moderate to severe tinea cruris were enrolled and all subjects completed this study. 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.

PK assessment: Plasma levels of circulating luliconazole and the Z-form metabolite were measured at the following time points:

- Subjects with tinea pedis:
  - Prior to study drug application on Days 1, 8, and 15
  - 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1, 8, and 15
- Subjects with tinea cruris:
  - Prior to study drug application on Days 1 and 8
  - 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1 and 8

Results:

In subjects with tinea pedis, the plasma concentrations of the metabolite z-luliconazole (15 to 250 times less active than the parent) were below the limit of quantification (i.e., <0.05 ng/mL) at all time points on Day 1. On Day 8 and Day 15, the mean z-luliconazole concentrations in all subjects were less than 0.1 ng/mL (range 0.03 to 0.08 ng/mL) at all time points. In subjects with tinea cruris, the mean plasma z-luliconazole concentrations were below the limit of quantification (i.e., <0.05 ng/mL) at all time points on Day 1 and Day 8 and as such are considered to be unreliable and any parameters "calculated" using these data points would be equally unreliable hence, they will not be reported in this review.

The Clinical Pharmacology Review comments that, based on the study report and the Agency analysis:

Tinea pedis:
This is 15 day treatment. Comparing the systemic exposure on Day 15 between adolescent and adults, the C_{max} and AUC_{0-24} in adolescent subjects was approximately 3.5 and 3.2 fold higher, respectively compared to adults.

Tinea cruris:
This is 8 day treatment. Comparing the systemic exposure on Day 8 between adolescent and adults, the C_{max} and AUC_{0-24} in adolescent subjects was approximately 2.7 and 2.5 fold higher, respectively compared to adults.

Clinical Pharmacology Reviewer's Recommendation: *NDA 204153/S-005 is acceptable from Clinical Pharmacology perspective. The recommended labeling changes will be in the final product labeling.*

5 Sources of Clinical Data

The current study investigated the safety and efficacy of Luliconazole Cream 1% in pediatric subjects aged 12 years to 17 years (inclusive) with tinea pedis and tinea cruris.

5.2 Review Strategy

The focus of this supplement will be on the single PK study.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Planned Clinical Study: MP-1010

Title: An Open-Label Study to Assess the Pharmacokinetics with Maximal Use of Luliconazole Cream 1% in Pediatric Patients with Moderate to Severe Tinea Pedis or Tinea Cruris

Objective: The objective of this study was to evaluate the pharmacokinetics with maximal use of Luliconazole Cream 1%, as measured by circulating plasma levels of luliconazole in adolescent patients ages 12 to < 18 years with moderate to severe interdigital tinea pedis or tinea cruris.

Study Design: This is an open-label PK study in adolescent subjects (aged 12 to < 18 years). Approximately 15 subjects with moderate to severe interdigital tinea pedis (as defined by a physician's global assessment [PGA] score of 2 or 3 involving both feet) and 15 subjects with moderate to severe tinea cruris (as defined by a PGA score of 2 or 3) were to be enrolled. Treatments were 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. Subjects with tinea pedis visited the clinic on study visit Days 1, 2, 8, 9, 15, and 16 where the study staff measured and the subject applied the study drug at the clinic on Days 1, 2, 8, 9, and 15.
Subjects with tinea cruris visited the clinic on study visit Days 1, 2, 8, 9 where the study staff measured and the subject applied the study drug at the clinic on Days 1, 2, and 8. At these visits, blood draws were taken for pharmacokinetic (PK) and safety assessments.

Number of Subjects: 30 (15 with tinea pedis; 15 with tinea cruris)

Ages of Subjects for Inclusion: 12 years to 17 years (inclusive)

Inclusion Criteria:

1. Subjects (or legal guardian/caregiver) with the ability and willingness to sign a written informed consent and/or assent (age appropriate).
2. Subject of either gender had to be at least 12 years to < 18 years of age (12 to 17 years, inclusive).
3. Subjects with a clinical diagnosis of moderate to severe tinea pedis, as defined by a PGA score of 2 or 3 on both feet or moderate to severe tinea cruris, as defined by a PGA score of 2 or 3
4. Subjects with a mycological diagnosis of tinea pedis or tinea cruris confirmed by the detection of fungal hyphae on a microscopic KOH wet mount.
5. Sexually active females of child-bearing potential (FOCBP) must have been willing to use:
    a. One of these highly effective contraception methods
        i. Intrauterine device (IUD); hormonal (injections, implants, transdermal patch, vaginal ring; tubal ligation; partner vasectomy,

    OR

    b. Oral contraceptives WITH a barrier method (listed below), OR
    c. Two barrier forms of contraception (listed below)
        i. Male or female condom; diaphragm with spermicides; cervical cap with spermicides; contraceptive sponge.

6. Subjects must have been in good general health and free of any disease that in the Investigator's opinion might interfere with the study evaluations.
7. Subjects/caregiver must have been able to communicate, able to understand the study procedures, and willing to comply with the study requirements.

Exclusion Criteria:

1. Subjects with both tinea pedis and tinea cruris.
2. Subjects with active atopic or contact dermatitis in the area to be treated.
3. Female subjects who were pregnant and/or nursing or planning a pregnancy during the course of the trial. Subjects who tested positive for pregnancy after start of test treatment were to be discontinued from test treatment but were to be followed for safety purposes.
4. Subjects who were immunocompromised (due to disease, eg, human immunodeficiency virus [HIV] or medications).
5. Subjects who had a recent history of or current drug or alcohol abuse.
6. Subjects with a history of intolerance or hypersensitivity to imidazole compounds or the inactive components of the study drug.
7. Subjects with current significant skin disease that was considered by the Investigator to be clinically important and indicative of conditions that might have complicated interpretation of study results.
8. Subjects with a life-threatening condition (eg, autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months.
9. Subjects with abnormal findings that were considered by the Investigator to be clinically important and indicative of conditions that might have complicated interpretation of study results.
10. Subjects with uncontrolled diabetes mellitus in the judgment of the Investigator.
11. Subjects/caregivers who were unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function.
12. Subjects who were currently in a clinical drug research study with other medications or had been a participant in a clinical trial within 30 days or 5 half-lives of the investigational drug (whichever was longer) prior to the Baseline visit.
13. Subjects with any other condition which, in the judgment of the investigator, would have put the subject at unacceptable risk for participation in the study, and
14. Subjects who were using the following medications;
    a. topical antifungal agent within 14 days of the Baseline visit (30 days for terbinafine, butenafine, and naftifine [topical]),
    b. systemic antifungal within 8 weeks or 5 half-lives of the antifungal (whichever was longer) prior to the Baseline visit (8 months for oral terbinafine),
    c. topical antibiotics within 30 days of the Baseline visit,
    d. systemic antibiotics within 30 days or 5 half-lives of the antibiotic (whichever was longer) prior to the Baseline visit,
    e. antibacterial soaps on the affected area within 1 week of the Baseline visit,
    f. topical corticosteroid in treatment area(s) within 14 days of the Baseline visit,
    g. systemic of intralesional corticosteroids within 30 days of the Baseline visit,
    h. any other medicated topical treatments to the treatment area(s) within 7 days of the Baseline visit,
    i. any other significant treatments, except hormonal contraception and multivitamins, at the discretion of the Investigator that would have interfered with study treatment.

Efficacy Assessments:
No efficacy assessments.

Pharmacokinetics:
Plasma levels of circulating luliconazole were measured at the following time points:

- Subjects with tinea pedis:
  - Prior to study drug application on Days 1, 8, and 15
  - 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1, 8, and 15

  Note: Samples for the 24-hour time points for Days 1, 8, and 15 were collected on Day 2, Day 9 (prior to study drug application), and Day 16, respectively.

- Subjects with tinea cruris:
  - Prior to study drug application on Days 1 and 8
  - 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1 and 8

  Note: Samples for the 24-hour time points for Days 1 and 8 were collected on Day 2 (prior to study drug application) and Day 9, respectively.

Safety Assessments:
At all visits, a safety evaluation and clinical grading will be performed. Local and systemic adverse event information will be collected, and blood will be drawn to obtain laboratory tests (chemistry, hematology, and urinalysis).

Reviewer's comment:
The protocol to this PMR was reviewed by the Agency. The safety assessments are acceptable.

6 Review of Efficacy

Efficacy Summary
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 completed.

6.1 Indication

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*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*, in patients 12 years of age and older for tinea pedis and tinea cruris and 2 years and older for tinea corporis.

6.1.1 Methods

Efficacy was not evaluated. See Agency Clinical Pharmacology Review for detail of the PK results.

6.1.2 Demographics

Demographics and baseline characteristics are presented in the tables below for the safety population.

Table 3: Summary of Demographic Characteristics (Safety Population)

	Tinea Pedis (N=15)	Tinea Cruris (N=15)	Total (N=30)
Age (years)			
mean (SD)	14.03 (2.17)	15.27 (1.49)	14.70 (1.91)
Min. To Max.	12.0, 17.0	12.0, 17.0	12.0, 17.0
Gender			
Male	13 (86.7)	10 (66.7)	23 (76.7)
Female	2 (13.3)	5 (33.3)	7 (23.3)
Ethnicity			
Hispanic or Latino	15 (100)	15 (100)	30 (300)
Not Hispanic or Latino	0	0	0
Race			
White	8 (53.3)	6 (40.0)	14 (46.7)
Black	6 (40.0)	7 (46.7)	13 (43.3)
Other	1 (6.7)	2 (13.3)	3 (10.0)

Source: Study report MP 1010

The overall mean age was 14.7 years and ranged from 12 years to 17 years. The mean age of the subjects was 14.13 years in the tinea pedis group and 15.27 years in the tinea cruris group. The majority of subjects in both treatment groups were male: 86.7% in the tinea pedis group and 66.7% in the tinea cruris group. Most of the subjects were of White race (53.3% and 40.0% in the tinea pedis and tinea cruris groups, respectively) or Black/African American race (40.0% and 46.7% in the tinea pedis and tinea cruris groups, respectively). One subject (6.7%) in the tinea pedis group and 2 subjects (13.3%) in the tinea cruris group were identified as "Other" for race. All of the subjects in both groups were of Hispanic or Latino ethnicity.

Reviewer's comment: *Subject's demographics are acceptable. The age ranges in this study is appropriate.*

6.1.3 Subject Disposition

There were no subject discontinuations. All 30 subjects completed the study.

Table 4: Subjects Disposition for MP 1011

	Tinea Pedis	Tinea Cruris	All
Subjects Enrolled	15	15	30
Completed	15	15	30
Discontinued	0	0	0

Source: table 14.1.1 MP-1010

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were explored.

Reviewer's Final Efficacy Conclusions: *No efficacy conclusions are made for this PK study.*

7 Review of Safety

Safety Summary
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).

Reviewer's comment: *The most notable aspect of the original NDA safety review for this application is the lack of significant safety issues. No systemic safety issues were reported. No safety issues which rise to the level of "Warnings and Precautions" were identified in the safety review of this supplement. This reviewer continues to recommend that "none" more accurately describes the possibility of severe reactions for Section 5, Warnings and Precautions for this supplement.*

7.1 Methods

A total of 30 subjects were described in the safety population for this study. Overall, 43 subjects had treatment-emergent adverse events (2 in tinea pedis and 1 in tinea cruris). There were no SAEs nor were there any TEAEs resulting in study discontinuation.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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).

7.1.2 Categorization of Adverse Events

Non-serious and serious AEs were monitored throughout the studies, and incidence, severity, timing, and relationship to administration of the study medication were collected for each AE or serious AE (SAE). Adverse events are coded to MedDRA (*version 14.0*).

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

None, this is a single clinical study.

7.2 Adequacy of Safety Assessments

This Phase 3 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.

Reviewer's comment: *In general, sufficient safety assessments were completed during this clinical trial to establish pediatric safety.*

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The amount of Luliconazole Cream 1% used by subjects in the tinea pedis group ranged from 17.6 grams to 33.6 grams. The amount of Luliconazole Cream 1% used by subjects in the tinea cruris group ranged from 19.4 grams to 27 grams.

7.2.2 Explorations for Dose Response

None

7.2.3 Special Animal and/or In Vitro Testing

Please see original NDA for a full non-clinical analysis.

7.2.4 Routine Clinical Testing

Study MP-1010 evaluated AEs at all visits, safety laboratory (hematology, chemistry, and urinalysis) at the designated time schedule, and urine pregnancy screening.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Certain classes of AEs were identified for other currently marketed antifungal products. To monitor safety in relation to these classes of AEs, listing for AEs that occurred on-study were reviewed by the applicant's clinical review team to identify those that were related to liver function abnormalities, kidney function abnormalities, and cardiac abnormalities that were considered AEs of special interest for this development program.

7.3 Major Safety Results

Table 5: Overall Summary of Adverse Events (Safety Population)

	Tinea Pedis (N=15)		Tinea Cruris (N=15)		Overall (N=30)	
	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects
Subjects with any AE	3	3 (20.0)	1	1 (6.7)	4	4 (13.3)
Subjects with any TEAE	2	2 (13.3)	1	1 (6.7)	3	3 (10.0)
Subjects with any SAE	0	0	0	0	0	0
Subjects with any TEAE leading to Withdrawal	0	0	0	0	0	0

AE = adverse event; TEAE = treatment-emergent AE; SAE = serious AE

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.

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

7.3.1 Deaths

No deaths were reported.

7.3.2 Nonfatal Serious Adverse Events

There were no SAEs reported in this clinical trial.

7.3.3 Dropouts and/or Discontinuations

No dropout or discontinuations were observed.

7.4 Supportive Safety Results

The supportive safety results showed few adverse events that were related to the treatment with luliconazole cream, 1%.

7.4.1 Common Adverse Events

The overall frequency of TEAEs was low in both treatment groups; 2 subjects (13.3%) in the tinea pedis group and 1 subject (6.7%) in the tinea cruris group. No individual TEAE occurred in more than a single subject in either treatment group or in the overall safety population. All of the TEAEs resolved on or within one day of the day of onset.

Table 6: Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Tinea Pedis N=15 n(%)	Tinea Cruris N=15 n(%)	Overall N=30 n(%)
Gastrointestinal disorders	**1 (6.7)**	**0**	**1 (3.3)**
Diarrhea	1 (6.7)	0	1 (3.3)
Infections and infestations	**0**	**1 (6.7)**	**1 (3.3)**
Naspharyngitis	0	1 (6.7)	1 (3.3)
Nervous system disorders	**1 (6.7)**	**0**	**1 (3.3)**
Headache	1 (6.7)	0	1 (3.3)

Note: Treatment-emergent adverse events are those with an onset after the initial application of luliconazole cream, 1%.
Source: Clinical Study Report, Table 14.3.2.1

Reviewer's comment: *The common AEs are mild in nature, none were moderate or severe.*

7.4.2 Laboratory Findings

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 differences between Luliconazole cream, 1% and vehicle cream.

7.4.3 Vital Signs

There was no pattern of change in the vital signs indicative of a safety signal or clinically meaningful difference between study drug and vehicle cream.

Reviewer's Conclusions:

- *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 tinea cruris, which are principally comprised of adolescents as tinea cruris and tinea pedis are both very uncommon in pre-pubertal children.*
- *There are no new safety issues from this PK clinical study. From this reviewer's perspective, this Supplement can be approved.*
- *The labeling will describe the safety profile of the study.*
- *Efficacy down to 12 years of age in tinea pedis and tinea cruris is extrapolated from the adult data for tinea pedis and tinea cruris.*

8 Postmarket Experience

Annual reports for luliconazole cream, 1% does not show any new significant safety issues.

9 Appendices

I. Physician Insert

9.2 Labeling Recommendations

The label presented in this section is the most current Agency recommended label. Final labeling will be available post-approval.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this topical product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GARY T CHIANG
01/25/2018

DAVID L KETTL
01/26/2018