CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204153Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	October 31st, 2013
From	Susan J. Walker, MD, FAAD
Subject	Division Director Summary Review
NDA #	NDA #204153
Applicant	Medicis Pharmaceutical Corporation
Date of Submission	December 11, 2012
PDUFA Goal Date	December 11, 2013
Proprietary Name / Established (USAN) names	Luzu/ luliconazole
Dosage forms / Strength	Cream/ 1%
Proposed Indication(s)	1. Interdigital Tinea pedis 2. Tinea cruris 3. Tinea corporis
Recommended:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gary Chiang, MD
CDTL Review	David Kettl, MD
Statistical Review	Yuqing Tang, PhD
Pharmacology Toxicology Review	Kumar D. Mainigi, MSc, PhD, MPH, DABT
ONDQA/CMC Review ONDQA Biopharm Review	Raymond P. Frankewich, PhD Kelly M. Kitchens, PhD
Clinical Microbiology Review	Simone M. Shurland, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD
OMP	Karen Dowdy, RN, BSN Kemi Asante, PharmD
OSE	Carlos M. Mena-Grillasca, RPh

OND=Office of New Drugs
CDTL=Cross-DisciplineTeam Leader
ONDQA=Office of New Drug Quality and Assessment
CMC =Chemistry, manufacturing and controls
OMP= Office of Medical Policy
OSE= Office of Surveillance and Epidemiology

1. Introduction

This application proposes the use of luliconazole cream, 1%, for the topical treatment of tinea pedis, tinea cruris, and tinea corporis. The review team recommends approval and there are no outstanding or controversial issues. This review will summarize the conclusions of the review team and include excerpts from the comprehensive cross-discipline team leader review by Dr. Kettl and the reviews of the team members listed above.

I concur with the team's recommendation for approval of luliconazole cream 1% 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. There are no outstanding issues from any review discipline, and draft labeling has been agreed upon with the applicant.

2. Background

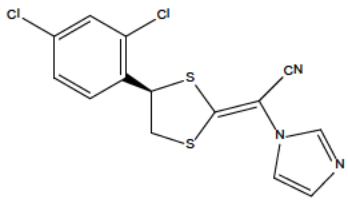
Luliconazole is a novel antimycotic agent in the azole class, a class which includes several approved drug products characterized by a five-membered aromatic nitrogen heterocyclic ring containing at least one other non-carbon atom. Luliconazole has been shown to share many basic chemical and biological characteristics with other azole antifungal agents. These azole antifungal compounds are generally considered to inhibit an enzyme (lanosterol demethylase) necessary for conversion of lanosterol to ergosterol. Ergosterol is a primary building block of the fungal cell wall, and depletion of ergosterol is disruptive to the integrity of the fungal cell wall and fungal growth.

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 inguinal area and adjacent skin. The most common organisms associated with this disease are *T. rubrum* and *E. floccosum*. Tinea corporis (ring worm) involves fungal infection of the arms, legs or trunk, especially on glabrous skin.

3. CMC/Device

LUZU (luliconazole) Cream, 1% contains 1% luliconazole, an azole antifungal agent, in a white cream for topical application. Luliconazole is (2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetonitrile. Its structural formula is:



The molecular formula is $C_{14}H_9Cl_2N_3S_2$ with a molecular weight of 354.28. Luliconazole is the R-enantiomer and contains one chiral center. The double bond adjacent to the dithiolane group is in the E configuration.

LUZU Cream, 1% contains 10 mg of luliconazole per gram of cream in a vehicle consisting of benzyl alcohol, butylated hydroxytoluene, cetostearyl alcohol, isopropyl myristate, medium-chain triglycerides, methylparaben, polysorbate 60, propylene glycol, purified water, and sorbitan monostearate.

Issues regarding pH consistency and precipitation of the drug substance were identified by the ONDQA chemistry reviewer, Dr. Ray Frankewich, in the course of the application review. These issues were adequately addressed and there are no outstanding concerns.

The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. The product will have an expiry date of 18 months. The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved.

I concur with the conclusions reached by the product quality reviewer that there are no outstanding CMC issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Dr. Kumar Mainigi, and no approvability issues were identified for this application.

The nonclinical safety profile for luliconazole cream is supported by nonclinical studies conducted in multiple species (mouse, rat, guinea pig, rabbit, and dog); most of these studies were conducted in Japan. The pivotal nonclinical studies were conducted under GLP conditions. The same studies were submitted in Japan to support the approval of Lulicon© cream and solution.

Luliconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosomal aberration assay) and one in vivo genotoxicity test (mouse bone marrow micronucleus test).

A fertility study in rats did not reveal any treatment related effects on fertility or reproductive function.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding preclinical issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted a maximal use PK trial in patients with tinea pedis and tinea cruris, incorporating areas of topical application that were more extensive than would usually be treated clinically. The mean AUC and C_{max} were somewhat higher in the patients with T. cruris, and this is consistent with the differential in topical bioavailability due to anatomic location.

Dr Shukla has fully evaluated the applicant's biopharmaceutics program. The applicant evaluated the inhibitory potential of luliconazole on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 using human liver microsomes. Luliconazole inhibited the enzymatic activities of all the five CYP enzymes and inhibitory activity was highest against CYP2C19 followed by CYP3A4.

Several CYP enzymes were not evaluated during the development program and included the inhibition potential of CYP2B6 and CYP2C8 which had been recommended by the Agency. I concur with the review conclusion that the potential of luliconazole to induce CYP enzyme activity would be unlikely to have any effect on luliconazole efficacy as the drug is directly administered to the target site (skin), where it is absorbed and then distributed into the plasma. However, the effect of induction potential (if any) of luliconazole on other drugs that are substrates of CYP1A2, 2B6 and 3A should to be adequately addressed as luliconazole may have the potential to affect the plasma levels of other drugs. These studies are detailed at the end of this review and can be conducted post-approval.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer and there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The clinical microbiology reviewer, Dr. Simone Shurland, concludes that from a clinical microbiology perspective, the information provided by the applicant supports the efficacy of luliconazole cream 1% for the treatment of tinea infections associated with the organisms *T. rubrum* and *E. floccosum*. (b) (4) Based upon the demonstrated antifungal activity of the drug product, labeling will include *T. rubrum* and *E. floccosum* (b) (4)

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical- Efficacy

The clinical program included one Phase 2 safety and efficacy trial and three Phase 3 safety and efficacy trials and one Phase 3 long term open label safety trial. The applicant has also submitted reports of Japanese trials as supporting information.

Tinea Pedis

The safety and efficacy of LUZU (luliconazole) Cream, 1% was evaluated in two randomized, double-blind, vehicle-controlled, multi-center clinical trials in 423 subjects with a clinical and culture-confirmed diagnosis of interdigital tinea pedis. Subjects were randomized to receive LUZU Cream, 1% or vehicle. Subjects applied either LUZU Cream, 1% or vehicle cream to the entire area of the forefeet including all interdigital web spaces and approximately 2.5 cm (1 in) of the surrounding area of the foot once daily for 14 days.

The mean age of the study population was 41 years; 82% were male; 53% were White and 40% were Black or African American. Signs and symptoms of tinea pedis (erythema, scaling, and pruritus), KOH exam and dermatophyte culture were assessed at baseline, end-of-treatment (Day 14), 2 and 4 weeks post-treatment.

Overall treatment success was defined as complete clearance (clinical cure and mycological cure) at 4 weeks post-treatment. LUZU Cream, 1% demonstrated complete clearance in

subjects with interdigital tinea pedis. Treatment outcomes at 4 weeks post-treatment are summarized in Table 1.

Table 1: Efficacy Results at 4 Weeks Post-treatment – Interdigital Tinea Pedis

	Study 1		**Study 2**	
	LUZU Cream, 1% N= 106 n (%)	**Vehicle Cream N= 103 n (%)**	**LUZU Cream, 1% N= 107 n (%)**	**Vehicle Cream N= 107 n (%)**
Complete Clearance[1]	28 (26%)	2 (2%)	15 (14 %)	3 (3%)
Effective Treatment[2]	51 (48%)	10 (10%)	35 (33%)	16 (15%)
Clinical Cure[3]	31 (29%)	8 (8%)	16 (15%)	4 (4%)
Mycological Cure[4]	66 (62%)	18 (18%)	60 (56%)	29 (27%)

[1] Proportion of subjects who achieved both clinical cure and mycological cure
[2] Negative KOH and culture and at most mild erythema and/or scaling and no pruritus
[3] Absence of erythema, scaling and pruritus
[4] Negative KOH and negative fungal culture

Tinea Cruris

The safety and efficacy of LUZU (luliconazole) Cream, 1% was evaluated in one randomized, double-blind, vehicle-controlled, multi-center clinical trial in 256 subjects with a clinical and culture confirmed diagnosis of tinea cruris. Subjects were randomized to receive LUZU Cream, 1% or vehicle. Subjects applied either LUZU Cream, 1% or vehicle cream to the affected area and approximately 2.5 cm (1 in) of the surrounding area once daily for 7 days.

The mean age of the study population was 40 years; 83% were male; 58% were White and 34% were Black or African American. Signs and symptoms of tinea cruris (erythema, scaling, and pruritus), positive KOH exam and dermatophyte culture were assessed at baseline, end-of-treatment (Day 7), 2 and 3 weeks post-treatment.

Overall treatment success was defined as complete clearance (clinical cure and mycological cure) at 3 weeks post-treatment. LUZU Cream, 1% demonstrated complete clearance in subjects with tinea cruris. Treatment outcomes at 3 weeks post treatment are summarized in Table 2.

Table 2. Efficacy Results at 3 Weeks Post-treatment - Tinea Cruris

	LUZU Cream, 1% N= 165 n (%)	Vehicle Cream N= 91 n (%)
Complete Clearance[1]	35 (21%)	4 (4%)
Effective Treatment[2]	71 (43%)	17 (19%)
Clinical Cure[3]	40 (24%)	6 (7%)
Mycological Cure[4]	129 (78%)	41 (45%)

[1] Proportion of subjects who achieved both clinical cure and mycological cure
[2] Negative KOH and culture and at most mild erythema and/or scaling and no pruritus
[3] Absence of erythema, scaling and pruritus
[4] Negative KOH and negative fungal culture

Tinea corporis

Agreement was reached that a total of three Phase 3 efficacy and safety trials, two for tinea pedis and one for tinea cruris, and supporting data, would be adequate to support the expanded indication of tinea pedis, tinea cruris, and tinea corporis in adults.

8. Safety

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

A total of 1495 subjects in the eleven US clinical studies (679 subjects with interdigital tinea pedis, 410 subjects with tinea cruris, 40 subjects with tinea corporis, and 426 healthy volunteers) applied luliconazole cream, 1% and were included in the safety population. The long- term study MP-1005 contributed 153 new subjects and 171 previous efficacy subjects who received vehicle cream in previous studies to the safety population.

In three Phase 3 clinical trials, 616 subjects were exposed to LUZU Cream, 1%: 305 with interdigital tinea pedis and 311 subjects with tinea cruris. Subjects with interdigital tinea pedis or tinea cruris applied LUZU Cream, 1% or vehicle cream once daily for 14 days or 7 days, respectively, to affected and adjacent areas. During clinical trials with LUZU Cream, 1% the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the LUZU and vehicle arms. Most adverse reactions were mild in severity.

The pre- and post-marketing international experience of luliconazole cream was considered as part of the application safety assessments. There were seven supportive Japanese clinical safety studies: one Phase 3 clinical study, three Phase 2 clinical studies, and three Phase 1 clinical studies. No significant safety signals have been identified in the Japanese trials. As of April 2011, approximately (b) (4) of luliconazole cream, 1%, were shipped in Japan, with an estimated 10.8 million patients exposed to luliconazole.

The clinical review by Dr. Gary Chiang concludes that there are no substantial safety issues associated with the topical use of luliconazole cream, and that most adverse reactions were application site reactions, and even those local reactions were judged to be mild and transient. No systemic safety issues were reported. The total safety database, both in clinical trials and in Japanese post-marketing experience, is more than sufficient to conclude that there are no

significant safety issues that would impact approval for this application.

I concur with Dr Chiang's conclusions and recommendations.

9. Advisory Committee Meeting

Although luliconazole is a new molecular entity, it was determined that this new topical azole antifungal cream presented no novel or complex scientific or regulatory issues that required advisory committee discussion. The drug substance is similar to several other antifungal products in structure and mechanism of action, and there are no concerns related to primary safety or efficacy determinations.

10. Pediatrics

The application triggers PREA as luliconazole is a New Molecular Entity and thus a new active ingredient requiring a pediatric study plan.

We are waiving the pediatric study requirement for ages 0 to 1 year 11 months for tinea corporis and for ages 0 to 11 years 11 months for tinea pedis and tinea cruris because necessary studies are impossible or highly impracticable. This is because these diseases are rare in the pediatric populations being waived.

We are deferring submission of pediatric studies for ages 2 years to 17 years 11 months for tinea corporis and for ages 12 years to 17 years 11 months for tinea pedis and tinea cruris for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. These required studies are listed below.

1 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.

2 A maximum use pharmacokinetic safety study in pediatric subjects 12 years to 17 years 11 months of age with interdigital tinea pedis and tinea cruris.

The applicant has agreed to conduct these studies and timelines have been determined.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

- The trade name of “Luzu” has been found acceptable.
- Physician labeling (PI) agreements have been reached.
- Patient Package Insert (PPI) “Patient Information” agreements have been reached.
- Carton-container labeling agreements have been reached.

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

Labeling is adequate to communicate necessary information to patients and prescribers

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, concurred by this Division Director summary review, is that safety and efficacy of luliconazole for adult interdigital tinea pedis, cruris and corporis is adequately supported by the development program. An approval action is recommended.

- Risk Benefit Assessment

The applicant has submitted sufficient information to demonstrate the efficacy and safety of Luzu Cream for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in adults, The safety findings are largely limited to local adverse events, with no serious adverse events deemed related to the proposed product.

The benefits of this product outweigh the risks when used as the prescribing information recommends for adults, and this Division Director summary review concurs that this application should be approved for patients > 17 years of age.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

REMS is neither required nor recommended for this topical antifungal product.

- Recommendation for other Postmarketing Requirements and Commitments

The following post marketing studies have been discussed with the applicant and agreements regarding study criteria and timelines have been reached.

Postmarketing Requirements

Required Pediatric Assessments:

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 subjects 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

Postmarketing Requirements under 505(o):

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.

Final Protocol Submission:	03/2014
Trial Completion:	04/2015
Final Report Submission:	12/2015

2101-4 Conduct 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 CYP2C19 substrate (PMR 2101-3) indicate no significant interaction.

Final Protocol Submission:	03/2016
Trial Completion:	04/2017
Final Report Submission:	12/2017

Postmarketing Commitments

Postmarketing Commitment under 506B:

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 the in vitro assessments.

Final Protocol Submission:	06/2014
Study Completion:	10/2014
Final Report Submission:	03/2015

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/s/

SUSAN J WALKER
11/14/2013