CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 3, 2013
From	David Kettl, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA #204153 Related IND: 76049
Applicant	Medicis Pharmaceutical Corporation
Date of Submission	December 11, 2012
PDUFA Goal Date	December 11, 2013
Proprietary Name / Established (USAN) names	Luzu (luliconazole) Cream 1%
Dosage forms / Strength	Cream, 1%
Proposed Indication(s)	1. Interdigital Tinea pedis 2. Tinea cruris 3. Tinea corporis
Recommended:	*Approval*

1. Introduction

The applicant, Medicis Pharmaceutical Corporation, submitted this application for luliconazole cream, 1%, for the proposed indications of tinea pedis, tinea cruris, and tinea corporis. The review team is in full concurrence that an approval recommendation is warranted for this product applied topically 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 adults ≥ 18 years of age.

The clinical review, by Dr. Gary Chiang, identified no significant safety or efficacy issues to impact the conclusion that sufficient evidence is provided in this application to reasonably demonstrate that the benefit of the drug product outweighs the risks when used according to the prescribing information. Most notably, adverse reactions were generally mild and were confined to application site reactions. No systemic adverse reactions are recommended for labeling, and no items are recommended for the Warnings and Precautions section of labeling.

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 (b) (4)

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 (b) (4) 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.

Additionally, 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. The clinical pharmacology team recommends in vivo drug interaction studies to be completed as post marketing studies as discussed below.

This CDTL review concurs with the team's recommendation of approving luliconazole cream 1% for the **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,** and concurs with the post marketing requirements discussed below. (b) (4)
There are no outstanding issues from any review discipline, and draft labeling has been agreed upon with the applicant.

2. Background

Proposed Indications:
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* (b) (4)

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,* (b) (4)

(b) (4) Tinea corporis involves fungal infection of the arms and legs, especially on glabrous skin; however it may occur on any part of the body.

Proposed Drug Product: Luliconazole
Luliconazole is an imidazole antifungal drug for the proposed topical treatment of tinea pedis, tinea cruris and tinea corporis in subjects (b) (4) years of age and older. The drug substance, luliconazole, is a New Molecular Entity (NME) proposed for topical application in a cream vehicle. Luliconazole has been shown to share many basic chemical and biological characteristics with azole class of antifungal agents.

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: (b) (4)
- Tinea versicolor

In Japan, as of April 2011, approximately (b) (4) of Lulicon® Cream, 1% and (b) (4) units Lulicon® Solution, 1% were shipped, with an estimated 10.8 million patients exposed to luliconazole. This international safety experience has been considered as part of the assessment for this application, and the adverse reaction experience is quite limited, with only two potential reactions, contact dermatitis, and cellulitis, recommended for addition to section 6.2 of the label, Postmarketing Events.

A Pre-IND meeting was conducted with the sponsor on January 16, 2007. The original IND 76049 to develop Luliconazole Cream, 1% to treat tinea pedis, tinea cruris, and tinea corporis was submitted by Janus Pharmaceuticals, Inc. on August 27, 2007. An End of Phase 2 meeting for the tinea pedis indication was conducted with the sponsor on December 16, 2009. An End of Phase 2 meeting for the tinea cruris and tinea corporis indications was conducted with the sponsor on October 27, 2010. SPA agreement letters for tinea pedis/cruris protocols were sent in 2010 and 2011. A Pre-NDA meeting was conducted with the sponsor on July 18, 2012.

3. CMC/Device

Two review issues were identified by the ONDQA chemistry reviewer, Dr. Ray Frankewich, in the course of the application review. Issues related to pH consistency (b) (4) of the luliconazole drug substance were resolved over the review cycle.

The pH of the drug product was found to (b) (4). The pH acceptance criterion in the drug product specification for the Japanese product and throughout clinical development in the U. S. has been 5.0 – 7.0.

Because of the issues with pH, the applicant has requested that the pH acceptance criterion in the drug product specification be expanded to (b) (4) This was not agreed to since there has been no clinical or CMC experience with a product the pH of which is (b) (4) In addition, the applicant's proposed expiration date of (b) (4) was not considered acceptable (b) (4) The applicant has agreed to the pH acceptance criterion of the drug product specification as 5.0 – 7.0. The applicant also agreed to change the proposed expiration dating period to 18 months.

The drug product marketed in Japan and manufactured in the U. S. exhibits (b) (4) when subjected to microscopic examination. It is stated in the NDA submission that the (b) (4)

Both of these issues were successfully resolved in discussions with the applicant, and the recommended expiry dating was agreed to be 18 months.

The drug product was initially developed and approved for use in Japan and has been commercially available since 2005. The formulation was not changed for the US clinical development program or for the proposed US commercial drug product, except for the grade of excipients (e.g., NF or USP versus JP).

There are 3 formulation manufacturing sites:

1. DPT, San Antonio, TX, USA

(b) (4)

(b) (4)

In the US clinical program, 9 out of 11 trials used the formulation manufactured by DPT (USA). The other 2 trials which include maximal use PK trial (MP-1007) and Phase 2 trial (TP-0801) used formulations manufactured by (b) (4)

The composition of the formulation from (b) (4) and DPT, USA are the same. During the manufacturing site change from Japan to US, there were minor process modifications which were classified as a Level 3 SUPAC SS change.

In vitro release tests (IVRT) were conducted as suggested in the SUPAC-SS guidance and results were submitted to demonstrate "sameness" of the products manufactured at two different locations. The in vitro drug release rate comparison data support the approval of the proposed drug product manufacturing site change, and the ONDQA Biopharmaceutics reviewer, Dr. Kelly Kitchens, recommends approval of the application.

The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved.

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

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. There are no outstanding issues from a chemistry perspective beyond completion of labeling negotiations.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Dr. Kumar Mainigi, who did not identify any approvability issues for this application. Agency recommended changes to proposed labeling have been agreed to by the applicant.

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.

Safety pharmacology studies were conducted in mice, rats, guinea pigs, rabbits, and dogs to investigate the effect(s) of luliconazole on the functioning of the central and autonomic nervous, respiratory and circulatory and renal systems. No significant treatment related effects were noted in these studies.

The general toxicity profile of luliconazole was evaluated in repeat dose toxicity studies conducted in rats and dogs. Dermal toxicity studies up to 4 weeks in rats and 26 weeks in dogs were conducted with luliconazole. Subcutaneous toxicity studies up to 26 weeks in rats were conducted with luliconazole. The primary target organ of toxicity identified in these studies was the liver. The primary toxicity noted in the liver was centrilobular hypertrophy of the liver possibly due to induction of metabolic enzymes. The liver toxicity was fully reversed after stopping drug administration.

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).

Subcutaneous reproductive and developmental toxicity studies were conducted with luliconazole in rats and rabbits. No treatment related effects were noted.

Luliconazole cream was a weak skin irritant in rabbits and the extent of dermal irritation did not increase after 28 days of repeat daily topical exposure compared to a single application. Luliconazole cream was a weak ocular irritant in rabbits. Luliconazole cream did not express

any phototoxic potential, sensitization potential, or photosensitization potential in male guinea pigs.

Conduct of a systemic carcinogenicity study was waived for luliconazole cream due to the limited systemic exposure noted under clinical conditions of use. The waiver for conduct of a dermal carcinogenicity study was granted based on the sponsor's submitted scientific rationale. The sponsor was informed on May 8, 2009 that a waiver from carcinogenicity studies was granted for luliconazole cream.

Overall, the nonclinical reviewer concurs that there is a margin of systemic safety based on animal toxicity data that is > 14 fold.

From a pharmacology/toxicology perspective, this application is approvable, as the nonclinical team concluded that the proposed clinical doses do not elicit any significant safety concerns.

5. Clinical Pharmacology/Biopharmaceutics

From a clinical pharmacology perspective, this application was found acceptable and no approvability issues were identified. However, the clinical pharmacology review by Dr. Chinmay Shukla notes that the CYP drug interaction assessments were not as comprehensive as the Agency had advised based on recommendations contained in the February, 2012 Drug Interaction Study guidance. Several post marketing studies, as listed below, are recommended to inform future labeling for luliconazole since the drug product is a new molecular entity.

The applicant conducted PK assessments in the following trials:

US trials:
- MP-1007 (Max use PK trial in subjects with tinea pedis or tinea cruris)
- MP-1000-08 (TQT trial)

Supporting Japanese trials:
- 113002 (Single topical dose PK assessment in healthy subjects)
- 113003 (Multiple topical dose PK assessment in healthy subjects)

The maximal use PK trial (MP-1007) was conducted in 30 adult subjects with moderate to severe interdigital tinea pedis (n=15) or moderate to severe tinea cruris (n=15). (Dr. Shukla notes that the overall contribution of tinea pedis to drug exposure appears to be small compared to drug exposure in subjects with tinea cruris.) All subjects received luliconazole cream, 1%, once daily in the morning for 15 days. The dose administered per application covered all affected and adjacent areas, including up to the ankle for tinea pedis and the groin, thighs, and abdomen for tinea cruris. The mean $AUC_{(0-t)}$ and C_{max} in subjects with tinea cruris following 8 days of once daily application were approximately 5.7 and 6.1 fold higher,

respectively, than the mean $AUC_{(0-t)}$ and C_{max} in subjects with tinea pedis following 15 days of once daily application.

Luliconazole was selectively manufactured as only the "R" enantiomer (native form) of the [redacted] (b) (4). Dr. Shukla comments that "Although the potential for inter-conversion between R to S enantiomer in vivo in humans would be useful to further characterize the PK of luliconazole, the available safety data from Phase 3 and the margin of systemic safety (> 14 fold) from animal toxicity studies are adequate to support the indication. Furthermore, the Sponsor noted that the R and S enantiomer had a similar toxicity profile with identical NOAEL values." No further information was deemed necessary for further characterization of chiral enantiomers.

The TQT trial (MP-1000-08) used the to-be-marketed formulation manufactured in USA. The results of the TQT trial were review by QT-IRT reviewer Dr. Qianyu Dang and according to Dr. Dang's review, luliconazole is not associated with QT prolongation.

No clinical trials were conducted to evaluate the effect of renal or hepatic impairment on the PK of luliconazole. This study is not justified given the > 14 fold margin of systemic safety based on the animal toxicity data and lack of systemic safety concerns from Phase 3 trials.

Regarding drug interaction assessments, 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. The clinical pharmacology team concluded that a positive result in any of these trials would not, in and of themselves, be a reason which could have precluded approval if the results were available during this first review cycle. Dr. Shukla's review notes that "*The potential of luliconazole to induce CYP enzyme activity would be unlikely to have any effect on luliconazole efficacy because; 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 needs to be adequately addressed as luliconazole might affect the plasma levels of other drugs.*"

The clinical pharmacology review concludes that the following post marketing studies be completed to fully inform prescribers in labeling as the product is an NME, and to address the pediatric issues for these antifungal indications. The clinical team concurs and the following will be presented to the sponsor at the Late Cycle Meeting:

Post-marketing requirements:

1. PK/Safety/Tolerability trial under maximal use conditions in subjects ages 12 years to 17 years 11 months with [redacted] (b) (4) tinea pedis and tinea cruris [redacted] (b) (4)

2. PK/Efficacy/Safety trial in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis.

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

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

Post-marketing commitments:

1. Conduct in-vitro assessment 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 assessment.

From a clinical pharmacology perspective, this application is acceptable pending agreements on recommended labeling changes, and the Post Marketing Requirements (PMR's) for both pediatric/adolescent studies and drug interaction studies.

6. Clinical Microbiology

The clinical microbiology review by 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 *T. rubrum* and *E. floccosum* in the treatment of tinea pedis and tinea cruris. (b) (4) No susceptibility testing interpretive criteria for luliconazole are recommended.

Like other imidazole anti-fungal agents, luliconazole inhibits the enzyme involved in the demethylation of the 14α position of lanosterol, which is necessary to convert lanosterol to ergosterol. Resistance to luliconazole has not been described.

Specific labeling related to causative organisms have been communicated and accepted by the applicant. There are no outstanding issues related to clinical microbiology.

7. Clinical/Statistical- Efficacy

The clinical program consisted of six Phase 1 trials which include a maximal use pharmacokinetic (PK) trial in subjects with moderate to severe tinea pedis or tinea cruris and PK assessment in TQT trial in healthy subjects, one Phase 2 safety and efficacy trial and three Phase 3 safety and efficacy trials and one Phase 3 long term open label long term safety trial. The Sponsor has also submitted reports of Japanese trials as supporting information and this includes three Phase 1 trials, three Phase 2 trials and one Phase 3 trial.

An End-of-Phase 2 meeting for tinea pedis was held with the sponsor on 12/16/2009, followed by a Special Protocol Assessment (SPA) for tinea pedis submitted on 5/24/2010. A SPA agreement letter for tinea pedis was sent on 7/7/2010. The applicant proposed to expand the indication to include tinea cruris and tinea corporis. The expanded indication was discussed at an additional End-of-Phase 2 meeting held on 10/27/2010. Agreement was reached that a total of three Phase 3 efficacy and safety trials, two for tinea pedis and one for tinea cruris, would be adequate to support the expanded indication of tinea pedis, tinea cruris, and tinea corporis. The applicant also obtained SPA agreements for the Phase 3 protocol for tinea cruris, with the SPA agreement letter for tinea cruris issued on 2/17/2011.

The findings from three pivotal trials, Study MP-1000-01 (Study 01) for subjects with tinea cruris, Study MP-1000-02 (Study 02) and Study MP-1000-03 (Study 03) for subjects with tinea pedis provide the primary basis for determination of efficacy.

The two tinea pedis studies were identical in design and evaluated subjects aged 12 years or older with clinical diagnosis of interdigital tinea pedis (moderate erythema, moderate scaling, and mild pruritus) on one or both feet, and positive KOH and fungal culture. Subjects with moccasin type tinea were excluded.

Study 01 evaluated subjects aged 12 years or older with clinical diagnosis of tinea cruris (moderate erythema, mild scaling, and moderate pruritus), and positive KOH and fungal culture.

The protocol specified primary endpoint was the proportion of subjects achieving “complete clearance” at Day 42 for tinea pedis and Day 28 for tinea cruris. “Complete clearance” was defined as both “mycological cure” (negative KOH and negative fungal culture) and “clinical cure” (scores of 0 on each individual signs for erythema, scaling, and pruritus).

Efficacy results based on the modified intent to treat (MITT) population with missing data imputed using the Last Observation Carried Forward (LOCF), and efficacy results based on

the per protocol (PP) population are presented in Table 1 from Dr. Yuqing Tang's Agency Biostatistical review. In all three studies, luliconazole cream 1% was demonstrated to be statistically superior to the vehicle cream.

Table 1. Results for Primary Efficacy Endpoint

	Luliconazole	Vehicle	Treatment Difference and its 95% Confidence Interval	*p*-value[3]
Tinea Cruris (Study 01)				
MITT[1] population	35/165 (21.2%)	4/91 (4.4%)	15.8%, (7.8%, 24.6%)	<0.001
PP[2] population	29/134 (21.6%)	3/68 (4.4%)	17.2%, (7.2%, 26.0%)	<0.001
Tinea Pedis (Study 02)				
MITT population	28/106 (26.4%)	2/103 (1.9%)	24.5%, (15.5%, 34%)	<0.001
PP population	26/88 (30.0%)	2/80 (2.5%)	27.0%, (16.4%, 38.1%)	<0.001
Tinea Pedis (Study 03)				
MITT population	15/107 (14.0%)	3/107 (2.8%)	11.2%, (3.7%, 19.5%)	<0.001
PP population	11/66 (16.7%)	2/60 (3.3%)	13.3%, (2.6%, 24.8%)	0.004

(1) MITT population was defined as all randomized subjects with positive baseline KOH and fungal cultures.
(2) PP population was defined as MITT subjects who completed end of treatment and post treatment evaluation without major protocol deviation. (3) *p*-value was calculated from CMH test stratified by center

The clinical review by Dr. Gary Chiang describes analyses of the variance of the efficacy results of the two tinea pedis trials. His review notes "The analysis shows that the discrepancy in the study effects between MP1-000-02 and MP-1000-03 was a random occurrence. The treatment effects across centers were generally consistent." Part of this difference may be due to practice variations in international (Central America) sites, though similar variability is seen in the recent Naftin Gel 2% approved labeling for the same indication of interdigital tinea pedis.

Subgroup analysis for the primary endpoint of "complete cure" was investigated for gender (male, female), Age (<median age, ≥median age), and race (white, black, other). There was a trend showing females with a higher success rate than males for tinea pedis. However, as approximately 82% of the subjects enrolled were male, the number of female subjects was too small to draw any reasonable conclusion. The younger age groups (<median age) showed a trend of higher response rate than the older age group (≥median age); however, this pattern was reversed for subjects with tinea cruris (Study 01). For efficacy by race, white subjects showed a small trend of higher response rate than Black subjects with tinea pedis.

For all three studies, most subjects were enrolled with moderate erythema, scaling, and pruritus. The response rate for these subjects was higher than subjects enrolled with severe erythema, scaling, and pruritus.

The drug product is applied topically. The applicant notes that the median total amount of product used per day in the Phase 3 study to assess the safety and efficacy of tinea cruris was 5.1 grams product per day.

The clinical and Biostatistical reviews both conclude that adequate demonstration of efficacy compared to vehicle gel has been provided in the application, and there are no outstanding issues related to efficacy. This CDTL review concurs with this recommendation, and draft labeling has been agreed to by the applicant for these indications.

8. Safety

The clinical review by Dr. Gary Chiang concludes that the most significant aspect of the safety review for this application is the lack of substantial safety issues beyond application site reactions, and even those local reactions that did occur were judged to be mild and transient. 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 application. As such, despite typical Agency advice to populate this section of approved labeling, this CDTL review concurs with the recommendation that "none" more accurately describes the possibility of severe reactions for the Warnings and Precautions section of labeling.

The clinical safety assessments during the Phase 3 clinical trials were adequate to establish short and long term safety. Minimal safety issues were identified and were confined to local application site reactions. The applicant also completed dermal safety studies and a single Phase 2 duration of use trial.

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% 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.

The only adverse reactions deemed reasonably associated with the use of luliconazole were application site reactions, and these were uncommon and did not differ significantly from vehicle cream. Labeling for Adverse Reactions in section 6.1 of labeling is recommended to be only:

> "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."

Systemic exposure demonstrated in the PK study, at doses three times the proposed clinical, dose did not induce higher adverse reactions. The TQT study did not demonstrate any potential to impact cardiac safety and no significant ECG changes were noted in the clinical trials.

A single death occurred in the development program. A 36 year old obese patient died of a heart attack and hypertension, but neither the applicant nor the clinical team concluded that this was related to the luliconazole treatment. None of the 11 serious adverse events that were observed were deemed related to the study medication.

Routine clinical laboratory and ECG testing did not identify any source of concerns for product safety.

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. In the post-market experience, one report of contact dermatitis and one report of cellulitis were classified as adverse drug reactions for in-patient treatment, and the two SAEs (vertigo and chordoma) were reported, but considered unrelated to luliconazole.

A review of the literature revealed two reports of contact dermatitis in Japan that were related to luliconazole treatment. In both cases, patch testing with the formulation components as well as luliconazole indicated the reactions were elicited by luliconazole re-challenge and resolved following withdrawal.

The 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.

9. Advisory Committee Meeting

Although luliconazole is a new molecular entity, it was determined early in the application review cycle that this new azole antifungal presented no novel or complex regulatory issues that required the input of the DODAC advisory committee. The active product is similar to several other antifungal products in structure and mechanism of action, and there were no concerns related to primary safety or efficacy determinations.

10. Pediatrics

The application triggers PREA as luliconazole is an NME and thus a new active ingredient requiring a pediatric study plan. The Pediatric Review Committee met on May 29 2013 to discuss the applicant's plan as well as waiver/deferral requests.

The applicant requested a partial waiver in pediatric subjects from birth to 1 year 11 months for tinea corporis and in pediatric subjects less than 12 years of age for tinea pedis and tinea cruris because studies are impossible or highly impractical in this population. The applicant has also requested for a deferral from conducting pediatric trials in subjects 2 to 17 years and 11 months old.

Specifically, the applicant has stated that they plan to conduct a maximal use PK trial in subjects 12 to 17 years and 11 months with tinea pedis and tinea cruris and a safety and efficacy trial including PK in subjects 2 to 17 years and 11 months with tinea corporis.

The pathophysiology and causative organisms for tinea pedis/cruris is similar in adolescents to adults. It does not seem necessary to demand efficacy data for the adolescent population, and efficacy can be reasonably extrapolated to adolescents. The applicant's rationale that tinea pedis is uncommon in pre-pubertal patients is reasonable, and a waiver for the population under 12 years of age is acceptable.

At a meeting with the Pediatric Review Committee (PeRC) on 05/29/2013, PeRC agreed to the partial waiver request in pediatric subjects from birth to 1 year 11 months for tinea corporis and in pediatric subjects less than 12 years of age for tinea pedis and tinea cruris. The Division also concurred with a partial deferral in pediatric patients 2 years to 17 years 11 months for tinea corporis and 12 years to 17 years 11 months for tinea pedis and tinea cruris because studies in adults are completed and the NDA application is being considered for approval in adults. PeRC agreed with the partial deferral request.

The applicant has agreed to address the pediatric requirement by conducting the following studies as post marketing requirements:

1. PK/Safety/Tolerability trial under maximal use conditions in subjects ages 12 years to 17 years 11 months (b) (4) with both tinea pedis and tinea cruris (b) (4)

2. PK/Efficacy/Safety trial in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis.

These studies are similar to several recent precedent approvals in the Division for antifungal products. 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.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are complete, and there are no outstanding issues impacting approval from the Office of Compliance. The Office of Compliance has issued an overall "Acceptable" recommendation.

Three study sites were selected for DSI inspection due to the relatively high treatment responders and large numbers of subjects enrolled. The DSI investigator noted some discrepancies between the total numbers of subjects enrolled at the sites and the mITT population. After discussions between the investigating team and the biostatistical team, it was determined that this would not affect the statistical conclusions rendered in the biostatistical review. The inspections were otherwise unremarkable.

12. Labeling

The trade name of "Luzu" has been accepted by DMEPA.

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 safety information to prescribers. The applicant has agreed with Agency proposed labeling, including carton/container labeling, as of the date of this CDTL review, and there are no outstanding issues related to labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, concurred by this CDTL 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

Efficacy for interdigital tinea pedis, tinea cruris, and tinea corporis in adults has been adequately demonstrated by the applicant. 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 CDTL review concurs that this application should be approved for patients > 17 years of age. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

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.

- Recommendation for other Postmarketing Requirements and Commitments

The rationale for the recommended PMR/PMC's is described above. The recommended PMR/PMC's which will be discussed at the Late Cycle Meeting are:

Post-marketing requirements:

1. PK/Safety/Tolerability trial under maximal use conditions in subjects ages 12 years to 17 years 11 months with (b) (4) with both tinea pedis and tinea cruris (b) (4)

2. PK/Efficacy/Safety trial in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis.

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

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

Post-marketing commitments:

1. Conduct in-vitro assessment 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 assessment.

There are no other recommended comments beyond the PMR/PMC's listed above. Draft labeling has been agreed to by the applicant.

- Recommended Comments to Applicant

There are no other recommended comments beyond the PMR/PMC's listed above. Draft labeling has been agreed to by the applicant.

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/s/

DAVID L KETTL
09/17/2013