CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204153Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 14, 2013
TO: NDA 204153 Luzu (luliconazole) Cream, 1%
Medicis Pharmaceutical Corporation

FROM: Julie Beitz, MD
Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Luzu (luliconazole) Cream, 1% is an azole antifungal product indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Tricophyton rubrum* and *Epidermophyton floccosum* in patients 18 years of age and older. For interdigital tinea pedis, luliconazole is applied once daily for two weeks; for tinea cruris and tinea corporis, luliconazole is applied once daily for one week.

This product was first developed and approved for use in Japan and has been marketed there since 2005. The drug product formulation was not changed for the US clinical development program or for the proposed US commercial drug product except for the grade of excipients. Luliconazole is a new molecular entity.

This memorandum documents my concurrence with the Division of Dermatology and Dental Product's (DDDP's) recommendation for approval of Luzu (luliconazole) Cream, 1%. Discussions regarding product labeling and postmarketing requirements and commitments have concluded and there are no inspectional issues that preclude approval.

REGULATORY HISTORY

A Pre-IND meeting was held on January 16, 2007 with Janus Pharmaceuticals, Inc. (with Catalyst Pharmaceutical Research, LLC as the US regulatory agent). Original IND 76049 to support clinical development of luliconazole for the treatment of interdigital tinea pedis was submitted on August 24, 2007, and received on August 27, 2007. On November 21, 2008, the US regulatory agent for the IND changed to Topica Pharmaceuticals, Inc.

An End-of-Phase 2 meeting regarding the interdigital tinea pedis indication was held on December 16, 2009, and was followed by submission of a Special Protocol Assessment (SPA) request on May 21, 2010 for review of the protocol that would support two identically designed trials in subjects with interdigital tinea pedis. An SPA Agreement letter was issued on July 7, 2010. On September 15, 2010, the IND was transferred to Medicis Pharmaceutical Corporation.

Medicis subsequently requested to expand the proposed indications for luliconazole to include tinea cruris and tinea corporis. This was discussed at an End-of-Phase 2 meeting held on October 27, 2010. Agreement was reached that a total of three Phase 3 efficacy and safety trials, two conducted in subjects with interdigital tinea pedis and one conducted in subjects with tinea cruris, would be adequate to support all three indications, namely, interdigital tinea pedis, tinea cruris, and tinea corporis. An SPA request was submitted on January 7, 2011 regarding the design of the Phase 3 tinea cruris trial and an Agreement letter was issued on February 17, 2011. A Pre-NDA meeting was held on July 18, 2012.

NDA 204153 was submitted on December 11, 2012. The application was reviewed under PDUFA V ("the Program") and granted a standard review. A Late Cycle Meeting was held with the applicant on September 11, 2013; as there were no substantive review issues, the meeting discussion focused primarily on postmarketing requirements. The application was not discussed before an FDA Advisory Committee as there were no novel or complex scientific or regulatory issues that required outside expertise. Luliconazole is an antifungal product in the azole class, a class which includes several approved products.

PRODUCT QUALITY

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 sobitan monostearate. It is packaged in (b) (4) aluminum tubes with white (b) (4) caps with trade sizes of 30 g and 60 g.

The pH of the drug product (b) (4) The pH acceptance criterion in the drug product specification for the Japanese product and throughout US clinical development has been 5.0 – 7.0. One of the (b) (4) in the drug product formulation is polysorbate 60. The Japanese product is manufactured using polysorbate 60 (b) (4) The US commercial product however will be manufactured using polysorbate 60 (b) (4)

The applicant requested that the pH acceptance criterion in the drug product specification be expanded to (b) (4) this was not deemed acceptable since there has been no clinical experience with a product with a pH (b) (4) In addition, the applicant's proposed expiration date of (b) (4) was not found acceptable (b) (4) The applicant has agreed to a pH acceptance criterion in the drug product specification of 5.0 – 7.0 and to an expiration dating period of 18 months.

NONCLINICAL

Luliconazole revealed no evidence of mutagenic or clastogenic potential based on the results of *in vitro* (Ames assay and Chinese hamster lung cell chromosomal aberration assay) and *in vivo* (mouse bone marrow micronucleus assay) genotoxicity testing. The Division granted the applicant a waiver for the conduct of carcinogenicity studies.

CLINICAL PHARMACOLOGY

Luliconazole is an azole antifungal product that appears to inhibit ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol. Luliconazole has been shown to be active against isolates of *Tricophyton rubrum* and *Epidermophyton floccosum* both *in vitro* and in clinical infections.

A maximal use pharmacokinetic trial to assess systemic exposure resulting from use of luliconazole was conducted in 12 subjects with moderate to severe interdigital tinea pedis and 8 subjects with moderate to severe tinea cruris. A mean daily amount of 3.5 g was applied to affected and surrounding areas for 15 days. Compared to subjects with interdigital tinea pedis, subjects with tinea cruris had higher values for C_{max} and AUC_{0-24}, consistent with anatomical differences in drug bioavailability.

Effects on QT interval. No evidence for QTc prolongation was noted in a thorough QT trial conducted in 66 healthy subjects. Exposures in this trial associated with a supratherapeutic dose (10 g) of luliconazole administered for 7 days exceeded exposures on day 15 in interdigital tinea pedis subjects under maximal use conditions. However, exposures with the supratherapeutic dose in the thorough QT trial did not exceed exposures on day 8 in tinea cruris patients under maximal use conditions.

Electrocardiograms were collected in interdigital tinea pedis and tinea cruris subjects under maximal use conditions and in the Phase 3 trial conducted in tinea cruris subjects. There were no adverse effects on cardiac repolarization noted in these subjects.

Drug interactions. The potential for luliconazole to inhibit CYP P-450 enzymes 1A2, 2C9, 2C19, 2D6, and 3A4 was evaluated *in vitro* using human liver microsomes. Luliconazole inhibited the enzymatic activities of all five CYP enzymes; inhibitory activity was highest against CYP2C19, followed by CYP3A4. In subjects with tinea cruris, luliconazole under maximal use conditions appeared to inhibit the activity of CYP2C19 and CYP3A4.

No *in vivo* drug interaction trials have been conducted to evaluate the potential of luliconazole inhibition of CYP2C19 and CYP3A4 to increase the exposure of co-administered drugs that are substrates of these CYP enzymes. The applicant will be required to conduct these trials under maximal use conditions in subjects with interdigital

tinea pedis and tinea cruris post-approval. In addition, the applicant has agreed to conduct *in vitro* assessments of 1) the inhibition potential of luliconazole for CYP2B6 and CYP2C8, and 2) the induction potential of luliconazole for CYP1A2, CYP2B6, and CYP3A in accordance with existing FDA guidance.[1]

Renal and hepatic impairment. No clinical trials have been conducted to evaluate the effect of renal or hepatic impairment on the pharmacokinetics of luliconazole. These studies are not deemed necessary given that available animal toxicity data provide for a greater than 14-fold margin of systemic safety and there are no serious safety concerns in the Phase 3 trial experience with luliconazole.

EFFICACY

The efficacy of Luzu (luliconazole) Cream, 1% was demonstrated in two randomized, double-blind, vehicle-controlled trials in subjects with interdigital tinea pedis, and in one randomized, double-blind, vehicle-controlled trial in subjects with tinea cruris. Historically, the Division's position has been that if efficacy is demonstrated in subjects with interdigital tinea pedis and tinea cruris, efficacy in tinea corporis is assumed due to similarities in the causative organisms among these topical fungal infections.

Interdigital tinea pedis. A total of 643 subjects, 12 years of age and older, with a clinical diagnosis of interdigital tinea pedis and positive KOH smear were randomized 1:1 to receive either Luzu Cream, 1% or vehicle cream in two trials with identical designs. Active or vehicle cream was applied to the entire area of the forefeet including all interdigital spaces and approximately 1 inch of the surrounding area of the foot once daily for 14 days. The mean daily amount of cream applied was 1.0 and 1.3 grams, respectively, in the two trials.

Efficacy was assessed 4 weeks after the last treatment (day 42) in those subjects with positive fungal cultures confirmed by a central mycology laboratory (i.e., the MITT population). In one trial, there were 106 luliconazole-treated and 103 vehicle-treated subjects in the MITT population. In the second trial, there were 107 luliconazole-treated subjects and 107 vehicle-treated subjects in the MITT population. The mean age of the subjects in these MITT populations taken together was 41 years; there were only 14 subjects < 18 years of age.

The protocol-specified primary endpoint was the proportion of subjects achieving "complete clearance". Complete clearance was defined as both "mycological cure" (negative KOH and negative fungal culture) and "clinical cure" (scores of 0 for erythema, scaling, and pruritus).[2]

Complete clearance was significantly higher in the luliconazole-treated groups compared to the vehicle-treated groups. The treatment difference (luliconazole vs. vehicle) was

[1] See *Guidance for Industry: Drug Interaction Studies - Study design, data analysis, implications for dosing, and labeling recommendations (published in draft, February 2012).*

[2] Possible scores ranged from 0 to 3 for none, mild, moderate, and severe, respectively.

25% and 11% in the two trials, respectively ($p < 0.001$ for both comparisons). Analysis of the variance in the efficacy results of the two trials was assessed, and the conclusion reached that the variance was due to chance.

Tinea cruris. A total of 483 subjects, 12 years of age and older, with a clinical diagnosis of tinea cruris and a positive KOH smear were randomized 2:1 to receive either Luzu Cream, 1% or vehicle cream. Active or vehicle cream was applied to the affected area and approximately 1 inch of the surrounding area once daily for 7 days. The mean daily amount of cream applied was 2.2 grams.

Efficacy was assessed as complete clearance at 3 weeks after the last treatment (day 28) in those subjects with positive fungal cultures confirmed by a central mycology laboratory (i.e., the MITT population comprising 165 subjects treated with luliconazole and 91 with vehicle). The mean age of the subjects in the MITT population was 40 years; there were only nine subjects < 18 years of age.

Complete clearance was significantly higher in the luliconazole-treated group compared to the vehicle-treated group. The treatment difference (luliconazole vs. vehicle) was 16% ($p < 0.001$).

SAFETY

A total of 616 subjects received luliconazole in the three Phase 3 trials submitted in the NDA (305 with interdigital tinea pedis and 311 with tinea cruris). In these trials, the most common adverse reactions were application site reactions. These occurred rarely, in less than 1% of luliconazole-treated and vehicle-treated subjects. Most adverse reactions were mild in severity.

In Japan, as of April 2011, an estimated 10.8 million patients had been exposed to luliconazole. Contact dermatitis and cellulitis have been reported and will be included in the **Postmarketing Experience** section of the product label.

The applicant conducted an open-label trial to assess the safety of recurrent treatments with luliconazole in subjects 12 years of age and older. The trial enrolled 581 subjects (187 subjects with tinea cruris, 354 with interdigital tinea pedis, and 40 with tinea corporis). Of these subjects, 153 were newly enrolled, 257 had received luliconazole in a previous Phase 3 trial, and 171 had received vehicle cream previously. No substantive differences were seen among subjects with interdigital tinea pedis, tinea corporis, or tinea cruris, or between initial and subsequent treatment courses.

PEDIATRICS

The **Pediatric Use** section of product labeling will state that the safety and effectiveness of Luzu Cream, 1% in pediatric patients have not been established. Too few subjects 12 years of age and older were enrolled in the Phase 3 trials to adequately assess safety and efficacy.

Historically the safety and efficacy of topical antifungal products such as luliconazole for the treatment of adults with interdigital tinea pedis and tinea cruris have been extrapolated to adults with tinea corporis. However, since the advent of the Pediatric Research Equity Act (PREA), pediatric studies demonstrating the safety and efficacy for topical antifungals are now required to support an indication for tinea corporis in the absence of other pediatric safety and efficacy information.

On May 29, 2013, the Pediatric Review Committee (PeRC) reviewed the applicant's partial waiver request in pediatric patients ages 0 to 1 year 11 months for tinea corporis, and for patients ages 0 to 11 years 11 months for interdigital tinea pedis and tinea cruris because necessary studies are impossible or highly impractable. This is because these diseases occur rarely in these pediatric subgroups. In addition, DDDP is 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 interdigital tinea pedis and tinea cruris for this application because this product is ready for approval in adults and the pediatric studies have not been conducted. The PeRC agreed with these actions.

The applicant will be required to conduct the following pediatric studies post-approval:

1) A multicenter, randomized, blinded, vehicle-controlled study, including pharmacokinetic assessments, with Luzu Cream, 1% for the treatment of tinea corporis in pediatric patients 2 years of age and older; and
2) A maximum use pharmacokinetic safety study in pediatric patients ages 12 years to 17 years 11 months with interdigital tinea pedis and tinea cruris.

TRADENAME REVIEW

On April 11, 2013, the applicant was notified by the Division of Medication Prevention and Analysis that the proposed tradename "Luzu" was acceptable.

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

/s/

JULIE G BEITZ
11/14/2013