

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204153Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO

NDA: 204153

Submission date: 12/11/2012

Drug: luliconazole (topical cream)

Applicant: Medicis Pharmaceutical Corporation

Indication: Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis

Reviewing Division: Division of Dermatology and Dental Products

Discussion:

The pharmacology/toxicology reviewer and supervisor recommended that this NDA could be approved for the indications listed above.

The applicant provided a sufficient nonclinical package to support approval. No carcinogenicity studies were conducted for luliconazole. The Division determined that this was acceptable based on information submitted by the applicant prior to NDA submission. Supporting information included low systemic bioavailability, lack of genotoxicity, lack of preneoplastic effects in chronic toxicity studies, lack of carcinogenic potential of similar molecules, anticipated intermittent use of the product and lack of clinical signals. While some of these reasons may not be sufficient to waive conduct of carcinogenicity studies, the overall weight of evidence was considered adequate.

Reproductive and developmental toxicity studies were conducted in rats and rabbits and showed only relatively minimal effects that will be described in labeling. A pregnancy category of C is appropriate.

The appropriate Established Pharmacologic Class for luliconazole is "Azole Antifungal", which is the same term used for other molecules in this class.

Conclusions:

I agree that this NDA can be approved from a pharmacology/toxicology perspective and that no additional nonclinical studies are needed. I agree with the labeling suggestions as outline in the primary and secondary pharmacology/toxicology reviews.

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/s/

PAUL C BROWN
08/07/2013

Pharmacology/Toxicology Supervisory Memorandum

NDA number: 204153
Supporting document: 1
CDER Stamp Date: December 11, 2012
Type of submission: Original NDA; 505(b)(1)
Applicant: Medicis Pharmaceutical Corporation
Supervisor name: Barbara Hill, PhD
Review Division: Dermatology and Dental Products
Date: July 30, 2013
Product: Luzu (luliconazole) Cream, 1%
Pharmacologic class: Azole antifungal
Indication: Interdigital Tinea Pedis, Tinea Cruris and Tinea Corporis

Cardiovascular Safety Pharmacology

A hERG assay was conducted with luliconazole. The effect of luliconazole (0.2 – 7.6 μM) on the hERG potassium current was assessed in HEK 293 cells. Luliconazole produced a concentration dependent inhibition of the potassium current. The IC_{50} for luliconazole in this assay was 1.52 μM . It is anticipated that the risk for QT interval prolongation for luliconazole would be minimal under clinical conditions of use due to minimal systemic exposure after topical application of luliconazole cream.

An in vivo cardiovascular safety pharmacology study was conducted in conscious telemetered dogs with luliconazole. No treatment related effects on electrocardiograms, blood pressure or heart rate were noted in this study after intravenous administration of 0.3, 1 and 3 mg/kg luliconazole.

I concur with the primary Pharmacology/Toxicology reviewer, Dr. Kumar D. Mainigi, that there is no cardiovascular safety concern for Luzu Cream based on the nonclinical data.

Repeat Dose Toxicity

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.

I concur with Dr. Mainigi's assessment that adequate nonclinical repeat dose toxicity studies have been conducted to support the safety of Luzu Cream.

Extractables Data

I concur with Dr. Mainigi's assessment that there are no Pharmacology/Toxicology concerns with the extractable data obtained for the container/closure system used for Luzu Cream.

Multiples of Human Exposure Calculations for the Label

To provide a maximum systemic exposure, all reproductive and developmental studies were conducted using the subcutaneous route. However, reliable AUC data could not be obtained in the subcutaneous reproductive and developmental studies conducted with luliconazole. Therefore, the multiples of human exposure for the reproductive and developmental toxicology studies described in the label are based on body surface area (BSA) comparisons. Based on conversations with the Clinical Reviewer, Dr. Gary Chiang, the maximum recommended human dose (MRHD) was set at 8 grams of 1% luliconazole cream per day for the tinea corporis indication. This is equal to 1.33 mg/kg/day luliconazole for a 60 kg individual ($80 \text{ mg luliconazole} \div 60 \text{ kg} = 1.33 \text{ mg/kg/day}$) or $49.2 \text{ mg/m}^2/\text{day}$ based on body surface area. The multiples of human exposure for the reproductive and developmental toxicity studies incorporated into the label based on body surface area comparisons are provided in the following table.

Study	Species	Route	NOAEL (mg/kg/day)	Body Surface Area Dose (mg/m ² /day)	Multiples of human exposure*
Fertility and general reproductive performance	Rats	Subcutaneous	1	6	0.1
Embryofetal study	Rats	Subcutaneous	25 ^a	150	3
			5 ^b	30	0.6
Embryofetal study	Rabbits	Subcutaneous	100	1200	24
Peri- and post-natal development study	Rats	Subcutaneous	25 ^c	150	3
			5 ^d	30	0.6

*Comparing to the human topical dose under maximum clinical use conditions: $49.2 \text{ mg/m}^2/\text{day}$, assuming 100% absorption.

a – NOAEL for maternal toxicity or malformations

b – NOAEL for skeletal variation

c – NOAEL for postnatal development

d – NOAEL for embryofetal toxicity

I concur with the recommended revisions for Sections 8.1 and 13.1 of the Luzu Cream label contained in Dr. Mainigi's review that have incorporated the multiples of human exposure based on BSA comparisons for the reproductive and developmental toxicity studies conducted with luliconazole.

Transfer of Luliconazole in Milk of Lactating Rats

A nonclinical pharmacokinetic study was conducted in lactating female rats administered a single subcutaneous injection of ¹⁴C-luliconazole. Radioactivity was detected in milk of lactating female rats after a single subcutaneous injection of ¹⁴C-luliconazole. The Luzu Cream label contains (b) (4)

Section 8.3 of the label. It is recommended that [REDACTED] (b) (4) be deleted from the label [REDACTED] (b) (4)

The proposed wording for Section 8.3 of the Luzu label is provided below. It is recommended that the ~~strikeout~~ text be removed from the label.

8.3 Nursing Mothers

It is not known whether luliconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Luzu Cream is administered to women who are breastfeeding.

[REDACTED] (b) (4)

Conclusions

- I concur with Dr. Mainigi's overall assessment that adequate nonclinical studies have been conducted to support the safety of Luzu Cream for the proposed indications.
- I concur that carcinogenicity assessment is not needed for this drug product (refer to detailed discussion contained in Dr. Mainigi's Pharmacology/Toxicology review for this drug product).
- I concur that there are no nonclinical approval issues for this drug product and that this NDA is approvable from a Pharmacology/Toxicology perspective.
- I concur that no nonclinical Post-Marketing Requirement studies are recommended for this NDA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Mainigi for Luzu Cream contained in section 1.3.3 of his review which include:
 - Pharmacologic Class designation of "azole antifungal"
 - Pregnancy Category C designation for this drug product
 - The revisions proposed for Section 8.1 of the label
 - The single sentence proposed for Section 12.1 of the label
 - The revisions proposed for Section 13.1 of this label
- In addition, I recommend that [REDACTED] (b) (4) be deleted from the label.

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/s/

BARBARA A HILL
07/30/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 204153
Supporting document/s: ORIG-1; SD-1
Applicant's letter date: December 11, 2012
CDER stamp date: December 11, 2012
Product: Luzu (luliconazole) Cream 1%
Indication: Treatment of interdigital tinea pedis, tinea cruris,
and tinea corporis
Applicant: Medicis Pharmaceutical Corporation
Dobson Road, Scottsdale, AZ 85256
Review Division: Dermatology and Dental Drug Products
Reviewer: Kumar D. Mainigi, Msc, PhD., M.P.H., DABT
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Susan Walker, M.D.
Project Manager: Cristina Attinello

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Luliconazole co-developed in 1994 by Nihon Nohyaku Company and Pola Chemical Industries, Inc. was approved in Japan on April 11, 2005 under the trade name "Lulicon©" (1% cream or liquid) for the treatment of tinea pedis, tinea corporis, tinea cruris, tinea versicolor and candidiasis, (b) (4)

Luliconazole (international nonproprietary name) is a new molecular entity in the United States. The azole anti-mycotic drug has a dithiolan structure produced by selectively synthesizing only the *R*-enantiomer at the chiral center. This (b) (4) is essentially the microbiologically active form. In Japan as of April 2011, approximately 10.8 million patients have been treated with approved luliconazole preparations.

Luliconazole Cream 1% (IND 76049) to treat tinea pedis was submitted by Janus Pharmaceuticals, Inc. on August 27, 2007. The New Drug Application to treat tinea pedis, tinea cruris, and tinea corporis was submitted by Medicis Pharmaceutical Corporation on December 11, 2012. The drug development is based on 11 clinical studies conducted in USA and Central America, and 7 Japanese clinical studies.

1.2 Brief Discussion of Nonclinical Findings

Luzu (luliconazole) cream, 1% is an azole antifungal agent being developed for the topical treatment of tinea pedis, tinea cruris, and tinea corporis. The comprehensive nonclinical safety profile for Luzu 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©.

Although, the clinical formulation is intended only for topical use, a number of parallel subcutaneous (intra-dermal injections) studies for greater drug exposure were also conducted. A few studies were conducted using the oral and peritoneal routes. In addition, phototoxicity, sensitization and photosensitization potentials were evaluated by more than one method.

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 pharmacokinetic profile of luliconazole was determined in vitro and in vivo after topical and subcutaneous administration in animals. The absorption rate after topical administration of the luliconazole cream was significantly greater in rats compared to

dogs. Luliconazole was distributed primarily to the liver and adrenal glands. No qualitative differences in the metabolic profile for luliconazole were noted in rats, dogs and humans based on in vitro studies.

To be marketed clinical formulation of Luliconazole Cream, 1% was used in most pharmacokinetic studies. After a single percutaneous application of ¹⁴C-luliconazole, 1% cream, C_{max} (0.134µg.eq/mL) in rats was achieved at T_{max} of 12 hours; drug was decreased below the detection limits (20ng/mL) at 168 hours. After seven daily applications of the same formulation, C_{max} was 3.3 times greater; however, elimination rate was similar to that observed after the single application. The percutaneous absorption rate for cream in rats was 13.6 percent; the rate of absorption in dogs was lower.

After single and multiple applications of cream formulation, radioactivity mainly resided on the application site in the horny layer of skin. There was almost no metabolism of luliconazole in the skin. Thus, no increase in plasma drug levels would be expected as a consequence of any enzyme inhibition.

In vitro microsomal assays, luliconazole inhibited a spectrum of CYP isoforms; most strongly inhibited was CYP2C19, followed by CYP3A4. However because of very high parent drug-plasma protein binding left a very low amount of free drug in the plasma, it is highly unlikely that any significant amount luliconazole will be available for metabolism and interactions with other drugs to alter their plasma concentrations.

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.

It was difficult to calculate the multiples of human exposure based on AUC comparisons for many of the nonclinical studies due to difficulties in obtaining an adequate pharmacokinetic profile in these studies. Therefore, the multiples of human exposure provided in the label are based on body surface area comparisons. Details concerning calculating the multiples of human exposure for the label are provided in Section 11 of this review. The sponsor included a table in the NDA submission that provided the multiples of human exposures based on AUC data derived from the 4 week dermal and subcutaneous toxicity study in rats and the 4 week dermal toxicity study in dogs. This table is presented in Section 11 with a discussion about its relevance for this topical drug product.

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 waiver for conduct of carcinogenicity studies was granted for luliconazole cream. Detailed information concerning the granting of this waiver request is provided in Section 8 of this review.

Subcutaneous reproductive and developmental toxicity studies were conducted with luliconazole in rats and rabbits. A subcutaneous fertility study, embryofetal development study and pre- and post-natal developmental study were conducted in rats with doses of 1, 5 and 25 mg/kg/day luliconazole.

In the rat fertility study, treatment related effects on reproductive function were noted in females (decreased live embryos and decreased corpus luteum) at 5 and 25 mg/kg/day and males (decreased sperm counts) at 25 mg/kg/day. No treatment related effects on fertility or reproductive performance were noted in rats at 1 mg/kg/day.

In the rat embryofetal development study, no treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day. However, increased incidences of skeletal variation (14th rib) were noted at 25 mg/kg/day. No treatment related effects on skeletal variation were noted at 5 mg/kg/day.

In the rat pre- and post-natal development study, maternal toxicity and embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day. No treatment related effects on postnatal development was noted at 25 mg/kg/day.

A subcutaneous embryofetal development study was conducted in rabbits with doses of 4, 20 and 100 mg/kg/day luliconazole. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day.

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.

A comprehensive nonclinical safety profile has been determined for luliconazole cream that supports the safety of the proposed clinical dosing regimen for the topical treatment of tinea pedis, tinea cruris and tinea corporis.

1.3 Recommendations

None

1.3.1 Approvability

Approvable with some modifications in the nonclinical sections of the label.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Luzu (luliconazole) Cream, 1% label reproduced below. The pharmacologic class designation for luliconazole for the treatment interdigital tinea pedis, tinea cruris, and tinea corporis is azole antifungal.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Luzu Cream is an ^{(b) (4)} azole antifungal indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, ^{(b) (4)} or *Epidermophyton floccosum*, in patients 18 years of age and older.

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of Luzu Cream in pregnant women.

^{(b) (4)}
Luzu Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose body surface area (BSA) comparisons (mg/m²) for the reproductive toxicology studies described in this section and in Section 13.1. The Maximum Recommended Human Dose (MRHD) was set at 8 g 1% cream per day (1.33 mg/kg/day for a 60 kg individual which is equivalent to 49.2 mg/m²/day).

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 7-17) to pregnant female rats. No treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons). Increased incidences of skeletal variation (14th rib) were noted at 25 mg/kg/day. No treatment related effects on

skeletal variation were noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons).

Subcutaneous doses of 4, 20 and 100 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 6-18) to pregnant female rabbits. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day (24 times the MRHD based on BSA comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered from the beginning of organogenesis (gestation day 7) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons). No treatment effects on postnatal development were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons).

12.1 Mechanism of Action

Luzu Cream is an azole antifungal [see *Clinical Pharmacology* (12.4)].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies ^{(b) (4)} to evaluate the carcinogenic potential of Luzu Cream have not been conducted.

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). ^{(b) (4)}

In a fertility study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered prior to and during mating and through early pregnancy. Treatment related effects on reproductive function were noted in females (decreased live embryos and decreased corpus luteum) at 5 and 25 mg/kg/day and males (decreased sperm counts) at 25 mg/kg/day. No treatment related effects on fertility or reproductive function were noted at 1 mg/kg/day (0.1X MRHD based on BSA comparisons).

2 Drug Information

2.1 Drug

CAS registry number: 187164-19-8

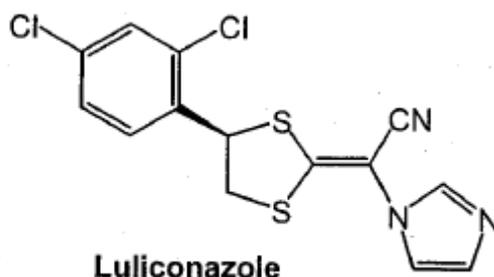
Generic name: Luliconazole

Code name: NND-502, PR-2699

Chemical name: (2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetonitrile

Molecular formula/molecular weight: C₁₄H₉Cl₂N₃S₂/354.28

Structure or Biochemical Description:



Pharmacologic Class: azole antifungal

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 76049; DMF (b) (4)

2.3 Drug Formulation

<u>Ingredient</u>	<u>Amount</u> (mg/g product)	<u>Function</u>
Luliconazole	10.0	Active agent
Cetostearyl alcohol	(b) (4)	(b) (4)
Isopropyl myristate		
Medium-chain triglyceride		
Polysorbate 60		
Sorbitan monostearate		
Benzyl alcohol		
(b) (4)		

(b) (4)
Propylene glycol
Purified water

(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The toxicity potential of some minor impurities (b) (4) and aged and photo-deteriorated drug products were tested for toxicity.

No toxicity was observed with (b) (4). Aged and photo-deteriorated luliconazole creams 1% tested as mild irritant, however, irritancy did not increase with the accelerated processes of aging or photodegradation. (b) (4) did not induce any reverse mutation in *S. typhimurium* and *E. coli* strains.

An extractables test was performed on the components of the container/closure system. Per the Chemistry review written by Raymond Frankewich, Ph.D. that was entered into DARRTS on July 16, 2013, the data from the extractables test complies with all applicable limits in 21 CFR 175.300 (c)(1) and (c)(3). There are no Pharmacology/Toxicology concerns with the extractable data obtained for the container/closure system used for this topical drug product.

2.6 Proposed Clinical Population and Dosing Regimen

Luzu Cream, 1% is administered topically for the treatment of intradigital tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, (b) (4) and *E. floccosum* in patients 18 years of age or older.

The maximum dosing regimen for the treatment of tinea pedis is 2 grams Luzu Cream per day for two weeks. The maximum dosing regimen for the treatment of tinea corporis is 8 grams Luzu Cream per day for one week. The maximum dosing regimen for the treatment of tinea cruris patients is 2 to 8 grams Luzu Cream per day, depending upon the size of affected area, for one week.

2.7 Regulatory Background

Luliconazole co-developed in 1994 by Nihon Nohyaku Company and Pola Chemical Industries, Inc. was approved in Japan in April 2005 under the trade name "Lulicon®" (1% cream or liquid) for the treatment of tinea pedis, tinea corporis, tinea cruris, tinea versicolor and candidiasis, (b) (4). This antimycotic azole is a new molecular entity in the United States that is being developed under the 505(b)(1) pathway.

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. A Pre-NDA meeting was conducted with the sponsor on July 18, 2012.

3 Studies Submitted

3.1 Studies submitted

All of the nonclinical studies submitted to IND 76049 were resubmitted to NDA 205153. A summary of the nonclinical studies conducted to support the safety of luliconazole cream is provided in this NDA review. The complete review of the nonclinical studies conducted to support the safety of luliconazole cream is provided under IND 76049.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

IND 76049

4 Pharmacology

4.1 Primary Pharmacology

The primary mechanism of action of luliconazole like several other approved azole antifungals involves inhibition of ergosterol biosynthesis. The primary target is the enzyme lanosterol 14 α -demethylase (CYP51, also called cytochrome P450_{DM}), the product of *ERG11* gene (Erg11p). A defective (inhibited) ERG 11p does not remove methyl groups at the 14 α carbon of ergosterol precursors, resulting in accumulation 14 α -methyl sterols, including 14 α -methyl-ergosta-8, 24(28)-dien-3 β , and 6 α -diol. These sterols because of their protruding methyl groups do not properly fit in the mosaic of membrane altering the fluidity and function of the plasma membrane, as a result fungal cells are more susceptible to oxygen-dependent microbicidal (fungicidal) systems of the host. In addition, the diol also accumulates in these cells. Frequently, fungal cells escape the destructive effects of 14 α -methyl sterols and diol due to a mutation in the enzyme sterol desaturase, the product of the *ERG3* gene.

The fungal mitochondria also contain high concentration of ergosterol, and its deficiency may also lead to dysfunctional enzymes. In addition, depletion of ergosterol may also interfere with the regulation of chitin synthesis, another component of the cell wall.

The primary mechanism of action for luliconazole was confirmed in studies using *Candida albicans* and *Trichophyton mentagrophytes*; in these organisms, drug caused inhibition of ergosterol synthesis at minimal inhibitory concentrations (MIC) of 0.014 μ M and 0.45nM, respectively. Luliconazole also inhibited the production of protease in *trichophyton* at a concentration (0.1ng/mL) that did not inhibit the growth, thus only inhibiting the progression of infection with dermatophytes in the horny layer. Electron microscopy revealed abnormal chitinase in the cell wall of *T. rubrum* at 1/1000 of the MIC, indicating the potential effect of drug on enzymes involved in the binding of chitin component to the cell wall and cytoplasmic membrane, and chitin synthesis in the cell wall.

In reconstituted human skin, luliconazole inhibited the invasion of *trichophyton* hypha at a concentration (0.1 μ g/mL) that did not inhibit the growth of the organism. The blocking of invasion was attributed to the inhibition of protease production by *trichophyton*.

4.2 Secondary Pharmacology

No studies were conducted.

4.3 Safety Pharmacology

Safety Pharmacology studies were conducted in mice, rats, guinea pigs, rabbits, and dogs to investigate the effect (s) of luliconazole on the functioning of central and autonomic nervous, respiratory and circulatory and renal systems.

Effects on the central nervous system: In all *in vivo* studies, luliconazole was administered subcutaneously.

After luliconazole administration (20, 200 and 2,000 mg/kg), mice were examined at 0.5, 2, and 4 hours according to Irwin's multi test observation (neurobehavioral and autonomic profiles) protocols. No drug related changes in behavior, and general activities were observed. In a similar study (30, 100, and 300mg luliconazole/kg), no significant differences in voluntary exercises between the drug treated and untreated animals were observed.

One hour after luliconazole administration (1, 3, and 10mg/kg), mice received an intraperitoneal injection of hexobarbital (80mg/10mL). The sleep induction time (i.e. time to the loss of the righting reflex) and sleeping time (i.e. the time of regaining the righting reflex) were determined. At the lowest dose of luliconazole, there was no effect on sleeping time; however, it significantly increased sleeping time at the mid- and high-dose levels. Accordingly, the prolongation of hexobarbital-induced sleep caused at the high-dose level of luliconazole was possibly due to the inhibition of drug metabolizing enzymes. There was no effect on the sleep induction time at any dose level.

At one hour post-dose (30, 100, and 300mg/kg), an electric shock was delivered to mice via electrodes attached to both the eye lids. The current at which clonic convulsions (CE) and tonic extensions (TE) first occurred were similar in the drug treated and control

animals. In a similar study, an hour after luliconazole administration (30, 100, and 300mg/kg), mice received 70mg/10mL of pentetrazol subcutaneously. CE and TE observed for 30 minutes did not reveal any difference between the drug treated and control animals, indicating lack of any drug synergism in pentetrazol-induced convulsions. In the next study, mice received the same dose of luliconazole with higher dose (110mg/10mL) of pentetrazol. Once again, no differences were observed in CE and TE, indicating lack of any drug antagonism in pentetrazol-induced convulsions.

The withdrawal threshold pressure was measured before and after administration of luliconazole (30, 100, and 300mg/kg) and at 0.5, 1, 2, and 4 hours post-dose in rats. A pressure analgesia meter applied to one hand paw of rat did not reveal any difference in threshold pressure in treated and non-treated animals. In another study, at the same dose levels and period of observation, luliconazole did not affect the body temperature of rats.

Effects on the autonomic nervous system and smooth muscle

Motility of isolated rabbit ileum hanged in Tyrode solution was measured using an isotonic transducer. Following the addition of luliconazole (10^{-6} , 10^{-5} , and 10^{-4} M), motility was measured for 10 minutes. A decrease in motility was observed at two high concentrations of drug. After washing luliconazole from the system, recovery of motility occurred at 10^{-5} M but not at 10^{-4} M.

In a similar study, after measuring the motility of guinea pig ileum, agonists (acetyl choline, histamine, BaCl₂, and 5-HT) were added five minutes after the addition of luliconazole. The effects of each drug concentration and each agonist on ileum contractions were measured. Luliconazole at 10^{-6} , 10^{-5} , and 10^{-4} M concentrations had no effect on contractions. At lowest concentration, luliconazole had no effect on contractions induced by agonists, however, inhibition of contractility was observed at the mid- and high concentrations of luliconazole.

Cardiovascular and pulmonary effects: Dogs surgically embedded with the telemetry transmitters and electrocardiograms received intravenous doses of 0.3, 1.0, and 3.0 mg luliconazole/kg. At various post-dose time points between 0.5 and 24 hours, electrocardiograms, blood pressure, heart and respiratory rates, and hemoglobin oxygen saturation were measured. None of the parameters were affected by luliconazole.

Gastrointestinal effects: To determine the gastrointestinal transport activity, mice after receiving subcutaneous doses of 30, 100, and 300mg luliconazole/kg were orally administered 0.1mL of carbon powder (5% suspension in 10% gum arabic). Animals were sacrificed after 30 minutes, and a lapotomy was conducted to determine the rate of transportation of carbon powder to the full length of the small intestine. Luliconazole had no significant effect on the gastrointestinal transport activity.

Renal effects: Immediately following subcutaneous doses (30, 100, and 300mg/kg) of luliconazole, rats received an oral dose of 2.5 mL saline/100g body weight. Urine collected for 6 hours was used to determine the concentration of electrolytes (Na⁺, K⁺, and Cl⁻). Urine volumes and electrolyte concentrations were similar in the treated and untreated rats which indicated no treatment related renal effects.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Pharmacokinetic studies were conducted in rats, dogs and humans using percutaneous, subcutaneous and intravenous routes of administration. The to-be-marketed clinical formulation of luliconazole cream, 1% was used in most of the topical pharmacokinetic studies. Some studies were conducted to compare the pharmacokinetic parameters of cream and solution formulations.

After a single percutaneous application of ¹⁴C-luliconazole, 1% cream, C_{max} (0.134µg.eq/mL) in rats was achieved at T_{max} of 12 hours; drug was decreased below the detection limit (20ng/mL) at 168 hours. After seven daily applications of the same formulation, C_{max} was 3.3 times greater; however, elimination rate was similar to that observed after the single application. The percutaneous absorption rate for cream in rats was 13.6 percent. In comparison, the rate of absorption in dogs after a single percutaneous application of ¹⁴C-luliconazole, 1% cream was low.

In rat percutaneous studies with the cream formulation, the peaks of radioactivity in most tissues were achieved at 12 hours. The largest amounts of radioactivity were found in the liver and adrenals, however, the concentration started to decrease after 24 hours. The patterns of tissue distribution and elimination of radioactivity were similar after the single and multiple applications, suggesting that any significant retention of drug and or its metabolites in the tissues was unlikely.

The metabolic profiles for luliconazole were investigated in the excreta (urine, feces, and bile) in rats and dogs and in vitro assays. The suggested pathway at an early stage starts with isomerization (Z-isomer), followed by cleavage of dithiolan ring leading to the formation of various conjugates, and eventually cleavage of imidazole ring to low molecular weight metabolites.

In an *in vitro* study using CYP-expressing microsomes, it was revealed that primarily two enzymes, CYP2D6 and CYP3A4, were involved in the metabolism of luliconazole, and the metabolites in animals and humans were similar. After single and multiple percutaneous applications of cream formulation in rats, radioactivity mainly resided on the application site in the horny layer of skin. There was almost no metabolism of luliconazole in the skin.

After a single percutaneous application of luliconazole cream 1% formulation to rats, 4.2 and 9.4% of the administered radioactivity was excreted in the urine and feces,

respectively, indicating bile as the major route of elimination. However, in dogs the amounts of radioactivity in the urine and feces were almost equal.

In another study, administration of radioactive bile from one set of rats to another set of rats confirmed the enterohepatic circulation of drug and its metabolites.

In vitro microsomal assays, luliconazole inhibited a spectrum of CYP isoforms; most strongly inhibited was CYP2C19, followed by CYP3A4. However because of very high parent drug-plasma protein binding leaving a very low amount of free drug in the plasma, it is highly unlikely that luliconazole will interact with other drugs to alter their plasma concentrations.

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

Single dose toxicity studies conducted in mice (subcutaneous and oral), rats (subcutaneous, oral and dermal), and dogs (dermal) indicated that the lethal dose was greater than 2,000mg/kg in all species. The histopathological examination of one dead female receiving oral dose of 2,000mg/kg revealed ground-glass-like regeneration, fibrosis and vacuolar degeneration in the liver.

6.2 Repeat-Dose Toxicity

Repeat dose toxicity studies were conducted in rats (4 week dermal toxicity study, 4 and 26 week subcutaneous toxicity studies) and dogs (4 and 26 week dermal toxicity studies). A 4 week dermal toxicity study in rats was conducted with once daily topical administration of luliconazole suspended in PEG 300 at doses of 0 (vehicle), 10, 50 and 250 mg/kg/day under occlusion. Four week and 26 week dermal toxicity studies in dogs were conducted with once daily topical administration of luliconazole suspended in PEG 300 at doses of 0 (vehicle), 5, 25 and 125 mg/kg/day under occlusion. A 4 week subcutaneous toxicity study in rats was conducted with once daily administration of luliconazole at doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day. A 26 week subcutaneous toxicity study in rats was conducted with once daily administration of luliconazole at doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 0.2, 1, 5 and 25 mg/kg/day.

Typically, repeat dose dermal toxicity studies are conducted with the clinical formulation of the topical drug product. However, it was determined that repeat dose dermal toxicity studies conducted with luliconazole suspended in PEG 300 were acceptable because they were conducted under a worst case scenario (i.e., under occlusion) and there were no novel excipients in the clinical formulation. Also, it would have been preferable if the chronic dermal toxicity study conducted in dogs had been a 9 month study instead of a 6 month study. However, it is understood that for the azole class of antifungal

drugs that the target organ of toxicity is the liver. This was confirmed in the 6 month dermal toxicity study conducted in dogs. Therefore, it was determined that conduct of a 9 month dermal toxicity study in dogs would not be needed for this topical drug product.

In the subchronic and chronic studies in rats (0.2.-250mg/kg/day) and dogs (5-125mg/kg/day), the liver was the primary target organ for luliconazole toxicity. The increased liver weights were associated with compensatory hypertrophy of the centrilobular hepatocytes; the lesion was attributed to the induction of drug metabolizing enzymes. No dermal irritation was noted in the repeat dose dermal toxicity studies conducted in rats and dogs.

The subcutaneous nodules and granulomas observed in subcutaneous studies were related to the retention of drug (white patches) substance under the injection sites.

In rat subcutaneous studies, the NOAEL was 5mg/kg/day after 4 weeks, and 1mg/kg/day after 26 weeks of dosing. In rats, the NOAEL was 250mg/kg/day after 4 weeks of percutaneous dosing. In dogs, the NOAEL of 25mg/kg/day was established both after 4 and 26 weeks of percutaneous treatment.

Refer to Section 11 for a table that provides the multiples of human exposure for the NOAELs identified in the 4 week dermal and subcutaneous toxicity studies in rats and in the 4 week dermal toxicity study in dogs.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Luliconazole was not mutagenic when tested at concentrations up to 5000 µg/plate in four histidine-requiring strains of *S. typhimurium* (TA98, TA100, TA1535 and TA1537) and one tryptophan-requiring strain of *E.coli* (WP2 $uvrA$).

7.2 *In Vitro* Assays in Mammalian Cells

Luliconazole was not clastogenic in a chromosomal aberration assay conducted at concentrations up to 150 µg/ml in Chinese hamster lung (CHL) cells.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Luliconazole was not clastogenic in a mouse bone marrow micronucleus assay at intraperitoneal doses up to 500 mg/kg/day administered on two consecutive days.

7.4 Other Genetic Toxicity Studies

None.

8 Carcinogenicity

The sponsor submitted a waiver request for conduct of carcinogenicity studies in the original IND submission. The scientific rationale provided by the sponsor for the waiver request is provided below.

- 1) A battery of required genotoxicity tests had revealed that both luliconazole and its (b) (4) were non-mutagenic and non-clastogenic.
- 2) In 26-week rat and dog subcutaneous studies intended to provide maximum drug exposure, histopathologic examinations did not reveal any pre-neoplastic lesions.
- 3) There is no evidence that any structurally related (to luliconazole) azole antifungal has produced malignant growths in animals.
- 4) The proposed period for clinical use of luliconazole cream 1% will not exceed 15 days. According to ICH guideline S1A (*The need for long-term rodent carcinogenicity studies of pharmaceuticals*), the carcinogenicity studies should be conducted for products to be used continuously for at least six months. In case of dermatologic products, the intermittent use for up to 6 months is also considered to be a valid reason to conduct carcinogenicity studies.
- 5) Although, the approved treatment period is 15 days, reportedly, repeated treatments with the clinical formulation for up to one year did not change the general safety profile of luliconazole.

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.

9 Reproductive and Developmental Toxicology

All studies were conducted using subcutaneous injections. The rat studies were conducted at dose levels of 0, 1, 5, and 25mg/kg/day. The rabbit study was conducted at dose levels of 0, 4, 20, and 100mg/kg/day.

9.1 Fertility and Early Embryonic Development

A subcutaneous fertility study was conducted with luliconazole in rats. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day were administered to males for four weeks prior to and through mating and to females for two weeks prior to mating through Gestation Day (GD) 7. At dose levels of 5 and 25mg/kg/day, some treatment related effects were observed on reproductive functions such as decreased sperm count noted in males at 25 mg/kg/day and decreased live embryos and decreased corpus luteum noted in females at 5 and 25

mg/kg/day. The NOAEL for the reproductive functions was 1mg/kg/day, the lowest dose tested.

9.2 Embryonic Fetal Development

A subcutaneous embryofetal development study was conducted with luliconazole in rats. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day were administered to pregnant female rats from GD 7 – 17. No treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day. Increased incidences of skeletal variation (14th rib) were noted at 25 mg/kg/day. No treatment related effects on skeletal variation were noted at 5 mg/kg/day. The NOAEL for fetal toxicity was 5 mg/kg/day.

A subcutaneous embryofetal development study was conducted with luliconazole in rabbits. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 4, 20 and 100 mg/kg/day were administered to pregnant female rabbits from GD 6 – 18. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day. The NOAEL for teratogenicity and fetotoxicity was 100mg/kg/day.

9.3 Prenatal and Postnatal Development

A subcutaneous pre- and post-natal development study was conducted with luliconazole in rats. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day were administered to pregnant female rats from GD 7 through Lactation Day (LD) 20. Maternal toxicity and embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day. No treatment related effects on postnatal development were noted at 25 mg/kg/day.

10 Special Toxicology Studies

Toxicity of analogues, metabolites and degradation products

In the single subcutaneous high-dose rat toxicity study, the (b) (4) (b) (4) (b) (4), did not cause any local or systemic toxicity at 2080 mg/kg.

Both the age- and photo-deteriorated luliconazole creams tested as mild skin irritants in rabbits. However, the intensity of the reaction was not enhanced with accelerated processes of aging or photo-deterioration.

In the subcutaneous rat study conducted at doses of 0, 1, 5, and 25mg/kg/day, the (b) (4) (b) (4) exhibited a toxicological profile very similar to luliconazole. (b) (4) was not mutagenic in an Ames assay and did not produce any chromosomal aberrations in the cultured Chinese hamster lung cells.

Local tolerance

Luliconazole cream 1% tested as a weak skin irritant in rabbits; however, the irritation was primarily attributed to the vehicle. In a 28-day rabbit dermal irritation study, slight erythema was noted after the first application of luliconazole cream and vehicle cream. Multiple applications of either the luliconazole cream or vehicle cream did not increase the dermal irritation noted after single application and did not produce cumulative irritation.

Both luliconazole and vehicle creams tested as weak ocular irritants in rabbits.

Luliconazole cream 1% did not express any phototoxic potential, sensitization potential (Buehler method, Adjuvant Patch test), or photosensitization potential (Adjuvant-Strip and Harber methods) when evaluated in male guinea pigs.

11 Integrated Summary and Safety Evaluation

The comprehensive nonclinical safety profile of Luzu (luliconazole) Cream, 1% 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 to support the approval of "Lulicon®" (1% cream or liquid) in Japan. All these nonclinical studies were submitted to and reviewed under IND 76049. No new nonclinical study reports were included in this NDA submission.

In addition to evaluating the toxicity profile of the parent drug in nonclinical studies, the general toxicity and genotoxicity potential of a major metabolite, (b) (4) and age- and photo-deteriorated drug products were also tested. The (u) (4) specification for the S-enantiomer in the drug substance was qualified per ICH Q3A and Q3B guidelines; this enantiomer was tested in general toxicology studies at levels up to (b) (4).

The dose selection in most animal studies was based on the preliminary dose range-finding studies. Although, the clinical formulation is intended only for topical use, a number of toxicity studies used the subcutaneous route of administration to achieve greater drug exposure. However, this approach to increase drug exposure somewhat interfered with the pharmacokinetic and toxicity profiles. In some animals, a portion of the injected drug product was deposited as a white patch under the injection site causing local reactions. This deposition of the drug product also caused the pharmacokinetic analysis for the subcutaneous studies to not be reliable due to the wide variability of plasma concentrations for the parent compound which did not allow determination of pharmacokinetic parameters in the low dose groups in many of the conducted nonclinical studies. Therefore, the multiples of human exposure calculated for the label were based on body surface area comparisons.

Safety pharmacology studies were conducted in mice, rats, guinea pigs, rabbits, and dogs to investigate the effect (s) of luliconazole on the functioning of central and autonomic nervous, respiratory and circulatory and renal systems.

An Irwin multi test (neurobehavioral and autonomic profiles) conducted in mice did not reveal any drug related changes in behavior at subcutaneous dose levels ranging from 20-2,000 mg/kg. The effect of luliconazole on hexobarbital induced sleep induction time (i.e., time to the loss of righting reflex) and sleeping time (i.e., the time of regaining the righting reflex) was evaluated in mice. Mice received intraperitoneal doses of 1, 3 and 10 mg luliconazole/kg one hour after receiving an intraperitoneal injection of 80mg/10mL of hexobarbital. Sleeping time was significantly increased at the mid- and high-dose levels. The prolongation of hexobarbital-induced sleep caused at the higher concentrations was possibly due to the inhibition of drug metabolizing enzymes. However, there was no effect on the sleep induction time at any dose level.

Dogs surgically embedded with the telemetry transmitters and equipment for electrocardiograms received intravenous doses of 0.3, 1.0, and 3.0 mg luliconazole/kg. At various post-dose points between 0.5 and 24 hours, electrocardiograms, blood pressure, heart and respiratory rates, and hemoglobin oxygen saturation were measured. None of the parameters were affected by luliconazole.

Luliconazole at subcutaneous dose levels of 30 – 300 mg/kg had no significant effect on the gastrointestinal transport activity in mice. At subcutaneous dose levels of 30 - 300mg/kg luliconazole, urine volumes and electrolyte concentrations were similar in the treated and untreated rats which indicated no treatment related renal effects.

The to-be-marketed clinical formulation of luliconazole cream, 1% was used in most of the pharmacokinetic studies. After a single percutaneous application of ¹⁴C-luliconazole, 1% cream, C_{max} (0.134µg.eq/mL) in rats was achieved at T_{max} of 12 hours; drug was decreased below the detection limits at 168 hours. After seven daily applications of the same formulation, C_{max} was 3.3 times greater; however, elimination rate was similar to that observed after the single application. The percutaneous absorption rate for cream in rats was 13.6 percent; the rate of absorption in dogs was lower.

In rat percutaneous studies with the cream formulation, the peaks of radioactivity in most tissues were achieved at 12 hours; the largest amounts were found in the liver and adrenals, however, the concentration started to decrease after 24 hours. The patterns of tissue distribution and elimination of radioactivity were similar after the single and multiple doses, suggesting that any significant retention of drug and or its metabolites in the tissues was unlikely.

No qualitative differences in metabolites between rats and dogs were observed. In a study using CYP-expressing microsomes, it was revealed that primarily two enzymes, CYP2D6 and CYP3A4, were involved in the metabolism of luliconazole, and the metabolites in animals and humans were similar. After single and multiple applications

of luliconazole cream formulation, radioactivity mainly resided on the application site in the horny layer of skin. There was almost no metabolism of luliconazole in the skin.

In human liver microsome assays, luliconazole inhibited the enzymatic activities of five CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D5, and CYP3A4); the inhibitory activity was greatest against CYP2C19. The ratio between the maximum concentration and K_i of free luliconazole ranged between 0.07-0.15 for CYP2C19 and 0.01-0.02 for CYP3A4, indicating very low potential of luliconazole for drug interactions. In addition, both animal and human pharmacokinetic data indicated lack of any trend for drug accumulation.

After a single percutaneous application of luliconazole cream 1% formulation to rats, 4.2 and 9.4% of the administered radioactivity was excreted in the urine and feces, respectively, indicating bile as the major route of elimination. In another study, administration of radioactive bile from one set of rats to another set of rats confirmed the enterohepatic circulation of drug and its metabolites.

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 luliconazole doses evaluated in the repeat dose dermal toxicity studies ranged from 10 – 250 mg/kg/day in rats and from 5 – 125 mg/kg/day in dogs. The luliconazole doses evaluated in the repeat dose subcutaneous toxicity studies ranged from 0.2 – 25 mg/kg/day in dogs. The primary target organ of toxicity identified in these studies was the liver. In both species, at the highest dose level, the microscopic findings were limited to centrilobular liver hypertrophy which is considered to be an adaptive response due to induction of drug metabolizing enzymes increasing metabolic activity. The liver toxicity was fully reversed after stopping drug administration. Nodules and granulomas found in almost all the subcutaneous studies were related to the retention of drug substance under the injection sites.

The sponsor has provided a tabulated summary of the multiples of human exposure at LOEL and NOAEL doses for the 4 week dermal toxicity studies in rats and dogs and the 4 week subcutaneous toxicity study in rats (refer to table below). The reference to “Margin of Safety” in the sponsor’s table below is the same as “Multiple of Human Exposure”.

The sponsor’s comparison between animal and human pharmacokinetic data is conservative. However, this comparison is complicated because of scanty percutaneous pharmacokinetic data in animals (low absorption). Some pharmacokinetic data was available for the 4 week studies summarized in the table below but pharmacokinetic data was not available for the 26 week subcutaneous toxicity study conducted in rats and the 26 week dermal toxicity study conducted in dogs. However, the multiples of human exposures provided in the table the sponsor included in the NDA submission do support the safety of luliconazole cream. It is anticipated that

the multiples of human exposure would be greater taking into consideration that liver hypertrophy is not an adverse effect but a transient adaptive response, no increase in toxicity was noted between the 4 week and 26 week toxicity studies, and the clinical conditions of use for each indication. Second, 0.5mg/kg dose in human was compared with 5mg/kg (NOAEL) dose in rats. Irrespective of uneven comparisons, a mean (M+F) margin of safety of 20 times was achieved.

Safety Margins of Luliconazole Cream 1% in Humans Relative to NOAEL and LOEL in Nonclinical General Toxicity Studies

Study	Species	Route	Dose LOEL mg/kg ²	Dose NOAEL mg/kg	Plasma Values ¹				Margin of Safety ⁴			
					LOEL Mean AUC		NOAEL Mean AUC		LOEL Mean AUC		NOAEL Mean AUC	
					M	F	M	F	M	F	M	F
4 wk	Rat	Topical	NA	250	NA	NA	205	662	NA	NA	1.9	6.2
4 wk	Rat	SC	25	5	5865	10147	1582	2826	54.8	94.9	14.8	26.4
4 wk	Dog	Topical	125	25	851	342	231	407	8.0	3.2	2.2	3.8
					Mean AUC							
			mg/dose	mg/kg ³	ng-hr/mL							
3 g Cream ⁵	Man	Topical	30	0.5	106.93		LLOQ = 0.05 ng/mL					
3 g Cream ⁶	Man	Topical	30	0.5	18.74							

LOEL = Lowest Effect Dose

NOAEL = No Observed Adverse Effect Dose

NA = Not applicable in this table since the highest dose was the NOAEL

1. LOQ = 20 ng/mL (except where noted)
2. Based on liver hypertrophy
3. Based on 60 kg human
4. Margin = Mean AUC_{animal}/Mean AUC_{human} (Tinea Cruris)
5. Tinea Cruris (8 day administration)
6. Tinea Pedis (15 day administration)

A NOAEL of 250mg/kg in rat topical study was reduced to a NOAEL of 5mg/kg in the subcutaneous study. In fact, NOAEL of 250mg/kg is a conservative approach for safety assessment since liver hypertrophy (LOEL) is not an adverse effect but a transient adaptive response. Therefore, more appropriate margin of safety (55-95 times) is achieved at subcutaneous LOEL (25mg/kg), especially in *tinea cruris* patients receiving maximum drug exposure (80mg luliconazole/day). The margin of safety will be much greater in case of *tinea pedis*.

The toxicity profiles of 4- and 26-week percutaneous studies in dogs were similar with a same NOAEL of 25mg/kg; no new toxicity was observed after six months of daily applications.

In a Phase I trial (Japan) where patients received daily topical applications of 5 grams of the clinical formulation for 7 days, the percutaneous absorption (calculated from the total excretion) was 5.4% after the first application, and 3.4% after the last application, i.e. a mean average absorption of 4.4%. The percutaneous absorption in humans is 1/3 of rats.

Taking into account, the realistic absorption rate of 4.4%, the maximum daily systemic exposure in human receiving 8grams cream per day will not exceed (2.2mg luliconazole/m²/day). At such low systemic exposure, azoles are not known to cause any serious adverse effects. In terms of body surface area using NOAEL of 1500mg/m²/day with 13.6% topical absorption, the margin of safety will be ~93 times. This value is also within the range of safety margin (55-95) tabulated at LOEL (table 1).

In the reverse mutation bacterial assay, luliconazole tested non-mutagenic. It also did not cause any chromosomal aberrations in the cultured mammalian cells, and was also non-clastogenic in the Mouse Micronucleus Test. Similarly, (b) (4) luliconazole tested non-mutagenic in a similar assay (Ames test), and also caused no structural damages or numerical changes in the chromosomal aberration assay in the mammalian cells.

A waiver for conduct of carcinogenicity studies was granted for luliconazole cream. Detailed information concerning the granting of this waiver request is provided in Section 8 of this review.

A complete ICH battery of subcutaneous reproductive and developmental studies were conducted with luliconazole. A subcutaneous fertility study was conducted with luliconazole in rats. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day were administered to males for four weeks prior to and through mating and to females for two weeks prior to mating through Gestation Day (GD) 7. At dose levels of 5 and 25mg/kg/day, some treatment related effects were observed on reproductive functions such as decreased sperm count noted in males at 25 mg/kg/day and decreased live embryos and decreased corpus luteum noted in females at 5 and 25 mg/kg/day. The NOAEL for the reproductive functions was 1mg/kg/day, the lowest dose tested.

A subcutaneous embryofetal development study was conducted with luliconazole in rats. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day were administered to pregnant female rats from GD 7 – 17. No treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day. Increased incidences of skeletal variation (14th rib) were noted at 25 mg/kg/day. No treatment related effects on skeletal variation were noted at 5 mg/kg/day. The NOAEL for fetal toxicity was 5 mg/kg/day.

A subcutaneous embryofetal development study was conducted with luliconazole in rabbits. Subcutaneous doses of 0 (vehicle: 0.5% sodium carboxymethylcellulose containing 0.1% Tween 80), 4, 20 and 100 mg/kg/day were administered to pregnant female rabbits from GD 6 – 18. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day. The NOAEL for teratogenicity and fetotoxicity was 100mg/kg/day.

A subcutaneous pre- and post-natal development study was conducted with luliconazole in rats. Subcutaneous doses of 0 (vehicle: 0.5% sodium

carboxymethylcellulose containing 0.1% Tween 80), 1, 5 and 25 mg/kg/day were administered to pregnant female rats from GD 7 through Lactation Day (LD) 20. Maternal toxicity and embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day. No treatment related effects on postnatal development were noted at 25 mg/kg/day.

To provide a maximum systemic exposure, all reproductive and developmental studies were conducted using the subcutaneous route. The sponsor proposed use of AUC based on (b) (4) to calculate the multiples of human exposure for teratogenicity in rats. This approach is not acceptable. The multiples of human exposure for the reproductive and developmental toxicology studies described in the label are based on body surface area (BSA) comparisons since reliable pharmacokinetic data could not be obtained in the subcutaneous reproductive and developmental studies. Based on conversations with the Clinical Reviewer, Dr. Gary Chiang, the maximum recommended human dose (MRHD) was set at 8 grams of 1% luliconazole cream per day for the tinea corporis indication. This is equal to 1.33 mg/kg/day luliconazole for a 60 kg individual (80 mg luliconazole ÷ 60 kg = 1.33 mg/kg/day) or 49.2 mg/m²/day based on body surface area. The multiples of human exposure for the reproductive toxicity studies incorporated into the label based on body surface area comparisons are provided in the following table.

In the rat teratogenicity study (0, 1, 5, and 25mg/kg/day), no maternal toxicity or changes in the reproductive functions were observed at the highest dose level (3 times the MRHD). Increased incidence of skeletal variation (14th rib) was observed at the highest dose level, but not at the mid-dose level (0.6 times MRHD). In rats, such skeletal at equivalent dose levels have also been observed for some approved azole antifungals such as ketoconazole; the effect seems to be species-specific.

In the rabbit teratogenicity study (0, 4, 20, and 100mg/kg/day) conducted at much higher dose levels, no skeletal variations and abnormalities in fetuses were observed. The NOAEL for teratogenicity and fetotoxicity was 100mg/kg/day (24 MRHD).

In a pre- and post-natal development study (0, 1, 5, and 25mg/kg/day) in rats, maternal and embryofetal (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) were observed at 25 mg/kg/day. No embryofetal toxicity was observed at 5 mg/kg/day (0.6 times the MRHD). No treatment related effects on postnatal development were recorded at 25 mg/kg/day (3 MRHD).

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.

A comprehensive nonclinical safety profile has been determined for luliconazole cream that supports the safety of the proposed clinical dosing regimen for the topical treatment of tinea pedis, tinea cruris and tinea corporis. This NDA is approvable from a Pharmacology/Toxicology perspective.

12 Appendix/Attachments

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/s/

DAIVENDER K MAINIGI
07/29/2013

BARBARA A HILL
07/29/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204-153 **Applicant:** MEDICIS

Stamp Date: 12-11-2012

Drug Name: Luzu Cream 1% **NDA/BLA Type:** 505(b)(1)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
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/s/

DAIVENDER K MAINIGI
01/30/2013

BARBARA A HILL
01/30/2013