

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204153Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUZU safely and effectively. See full prescribing information for LUZU.

LUZU (luliconazole) Cream, 1% for topical use
Initial U.S. Approval: 2013

-----**INDICATIONS AND USAGE**-----
LUZU (luliconazole) Cream, 1% is an azole antifungal indicated 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. (1)

-----**DOSAGE AND ADMINISTRATION**-----
For topical use only. Not for ophthalmic, oral or intravaginal use. (2)

Interdigital Tinea Pedis: LUZU Cream, 1% should be applied to the affected and immediate surrounding area(s) once a day for two weeks. (2)

Tinea Cruris and Tinea Corporis: LUZU Cream, 1% should be applied to the affected skin and immediate surrounding area(s) once a day for one week. (2)

-----**DOSAGE FORMS AND STRENGTHS**-----
Cream, 1% (3)

-----**CONTRAINDICATIONS**-----
None. (4)

-----**ADVERSE REACTIONS**-----
The most common adverse reactions observed in clinical trials were application site reactions, which occurred in less than 1% of subjects. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Medicis, a division of Valeant Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUZU (luliconazole) Cream, 1% is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For topical use only. LUZU Cream, 1% is not for ophthalmic, oral, or intravaginal use.

- When treating interdigital tinea pedis, a thin layer of LUZU Cream, 1% should be applied to the affected area and approximately 1 inch of the immediate surrounding area(s) once daily for two (2) weeks.
- When treating tinea cruris or tinea corporis, LUZU Cream, 1% should be applied to the affected area and approximately 1 inch of the immediate surrounding area(s) once daily for one (1) week.

3 DOSAGE FORMS AND STRENGTHS

Cream, 1%. Each gram of LUZU Cream, 1% contains 10 mg of luliconazole in a white cream base.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

6.2 Post-Marketing Experience

The following adverse reactions have been identified during postmarketing use of luliconazole cream, 1%: contact dermatitis and cellulitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

The potential of luliconazole to inhibit cytochrome P-450 (CYP) enzymes 1A2, 2C9, 2C19, 2D6, and 3A4 was evaluated in vitro. Based on in vitro assessment, luliconazole at therapeutic doses, particularly when applied to patients with moderate to severe tinea cruris, may inhibit the activity of CYP2C19 and CYP3A4. However, no in vivo drug interaction trials have been conducted to evaluate the effect of luliconazole on other drugs that are substrates of CYP2C19 and CYP3A4.

Luliconazole is not expected to inhibit CYPs 1A2, 2C9 and 2D6 based on in vitro assessment. The induction potential of luliconazole on CYP enzymes has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of LUZU Cream, 1% in pregnant women. LUZU Cream, 1% 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/m^2) 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 $\text{mg}/\text{kg}/\text{day}$ for a 60 kg individual which is equivalent to 49.2 $\text{mg}/\text{m}^2/\text{day}$).

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 1, 5 and 25 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (3 times the MRHD based on BSA comparisons). Increased incidences of skeletal variation (14th rib) were noted at 25 $\text{mg}/\text{kg}/\text{day}$. No treatment related effects on skeletal variation were noted at 5 $\text{mg}/\text{kg}/\text{day}$ (0.6 times the MRHD based on BSA comparisons).

Subcutaneous doses of 4, 20 and 100 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (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 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$. No embryofetal toxicity was noted at 5 $\text{mg}/\text{kg}/\text{day}$ (0.6 times the MRHD based on BSA comparisons). No treatment effects on postnatal development were noted at 25 $\text{mg}/\text{kg}/\text{day}$ (3 times the MRHD based on BSA comparisons).

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, 1% is administered to women who are breastfeeding.

8.4 Pediatric Use

The safety and effectiveness of LUZU Cream, 1% in pediatric patients have not been established. The number of pediatric patients ≥ 12 years of age were too small to adequately assess safety and efficacy.

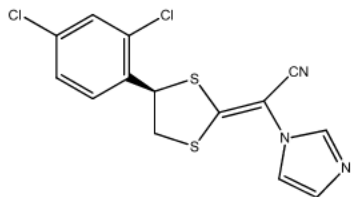
8.5 Geriatric Use

Of the total number of subjects in clinical studies of LUZU Cream, 1%, 8 percent were 65 and over, while 1.4 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

LUZU (luliconazole) Cream, 1% contains 1% luliconazole, an azole antifungal agent, in a white cream for topical application.

Luliconazole is (2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetonitrile. Its structural formula is:



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LUZU Cream, 1% is an azole antifungal [see *Clinical Pharmacology* (12.4)].

12.2 Pharmacodynamics

At therapeutic doses, LUZU Cream, 1% is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Luliconazole is the R enantiomer of a chiral molecule. The potential for inter-conversion between R and S enantiomers in humans has not been assessed. Information on the pharmacokinetics of luliconazole presented below refers to both R enantiomer and S enantiomer, if any, combined.

Luliconazole is >99% protein bound in plasma.

In a pharmacokinetic trial, 12 subjects with moderate to severe tinea pedis and 8 subjects with moderate to severe tinea cruris applied a mean daily amount of approximately 3.5 grams of LUZU Cream, 1% to the affected and surrounding areas once daily for 15 days. Plasma concentrations of luliconazole on Day 15 were measurable in all subjects and fluctuated little during the 24 hour interval. In subjects with tinea pedis, the mean \pm SD of the maximum concentration (C_{max}) was 0.40 ± 0.76 ng/mL after the first dose and 0.93 ± 1.23 ng/mL after the final dose. The mean time to reach C_{max} (T_{max}) was 16.9 ± 9.39 hours after the first dose and 5.8 ± 7.61 hours after the final dose. Exposure to luliconazole, as expressed by area under the concentration time curve (AUC_{0-24}) was 6.88 ± 14.50 ng*hr/mL after the first dose and 18.74 ± 27.05 ng*hr/mL after the final dose. In subjects with tinea cruris, the mean \pm SD C_{max} was 4.91 ± 2.51 ng/mL after the first dose and 7.36 ± 2.66 ng/mL after the final dose. The mean T_{max} was 21.0 ± 5.55 hours after the first dose and 6.5 ± 8.25 hours after the final dose. Exposure to luliconazole, as expressed by AUC_{0-24} was 85.1 ± 43.69 ng*hr/mL after the first dose and 121.74 ± 53.36 ng*hr/mL after the final dose.

12.4 Microbiology

Mechanism of Action

Luliconazole is an antifungal that belongs to the azole class. Although the exact mechanism of action against dermatophytes is unknown, luliconazole appears to inhibit ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity by azoles results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol.

Mechanism of Resistance

To date, a mechanism of resistance to luliconazole has not been described.

LUZU Cream, 1% has been shown to be active against most isolates of the following fungi, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:

Trichophyton rubrum
Epidermophyton floccosum

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of LUZU Cream, 1% 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).

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).

14 CLINICAL STUDIES

14.1 Interdigital Tinea Pedis

The safety and efficacy of LUZU (luliconazole) Cream, 1% was evaluated in two randomized, double-blind, vehicle-controlled, multi-center clinical trials in 423 subjects with a clinical and culture-confirmed diagnosis of interdigital tinea pedis. Subjects were randomized to receive LUZU Cream, 1% or vehicle. Subjects applied

either LUZU Cream, 1% or vehicle cream to the entire area of the forefeet including all interdigital web spaces and approximately 2.5 cm (1 in) of the surrounding area of the foot once daily for 14 days.

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

Overall treatment success was defined as complete clearance (clinical cure and mycological cure) at 4 weeks post-treatment. LUZU Cream, 1% demonstrated complete clearance in subjects with interdigital tinea pedis. Treatment outcomes at 4 weeks post-treatment are summarized in Table 1.

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

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

¹ Proportion of subjects who achieved both clinical cure and mycological cure

² Negative KOH and culture and at most mild erythema and/or scaling and no pruritus

³ Absence of erythema, scaling and pruritus

⁴ Negative KOH and negative fungal culture

14.2 Tinea Cruris

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

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

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

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

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

¹ Proportion of subjects who achieved both clinical cure and mycological cure

² Negative KOH and culture and at most mild erythema and/or scaling and no pruritus

³ Absence of erythema, scaling and pruritus

⁴ Negative KOH and negative fungal culture

16 HOW SUPPLIED/STORAGE AND HANDLING

LUZU (luliconazole) Cream, 1% is a white cream supplied in tubes as follows:

30 g (NDC 99207-850-30)

60 g (NDC 99207-850-60)

Store at 20 C to 25 C (68 F to 77 F); excursions permitted from 15 C -to 30 C (59 F to 86 F) [*see USP Controlled Room temperature*].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Inform patients that LUZU Cream, 1% is for topical use only. LUZU Cream, 1% is not intended for intravaginal or ophthalmic use.

Manufactured for:

Medicis, a division of Valeant Pharmaceuticals, Bridgewater, NJ 08807

Manufactured by:

DPT Laboratories, Ltd., San Antonio, TX 78215

PATIENT INFORMATION
LUZU (loo-zoo)
(Iuliconazole) Cream, 1%

Important information: LUZU Cream is for use on skin only. Do not get LUZU Cream near or in your eyes, mouth or vagina.

What is LUZU Cream?

LUZU Cream is a prescription medicine used on the skin (topical) to treat athlete's foot that is between the toes (interdigital tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis) in people 18 years of age and older.

It is not known if LUZU Cream is safe and effective in children.

What should I tell my doctor before using LUZU Cream?

Before using LUZU Cream, tell your doctor about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if LUZU Cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUZU Cream passes into your breast milk.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use LUZU Cream?

- Use LUZU Cream exactly as your doctor tells you to use it.
- If you have athlete's foot (tinea pedis), apply a thin layer of LUZU Cream to the affected skin areas and to about 1 inch of the surrounding healthy skin 1 time a day for 2 weeks.
- If you have jock itch (tinea cruris) or ringworm (tinea corporis), apply LUZU Cream to the affected skin areas and to about 1 inch of the surrounding healthy skin 1 time a day for 1 week.
- Wash your hands after you apply LUZU Cream.

What are the possible side effects of LUZU Cream?

LUZU Cream may cause skin reactions at the treatment site. Skin irritation may happen with LUZU Cream. Tell your doctor if you have any skin reactions on the areas of your skin treated with LUZU Cream.

These are not all the possible side effects of LUZU Cream.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LUZU Cream

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or doctor for information about LUZU Cream that is written for health professionals. Do not use LUZU Cream for a condition for which it was not prescribed. Do not give LUZU Cream to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in LUZU Cream?

Active ingredient: Iuliconazole

Inactive ingredients: benzyl alcohol, butylated hydroxytoluene, cetostearyl alcohol, isopropyl myristate, medium-chain triglycerides, methylparaben, polysorbate 60, propylene glycol, purified water, sorbitan monostearate

Manufactured for: Medicis, a division of Valeant Pharmaceuticals, Bridgewater, NJ 08807

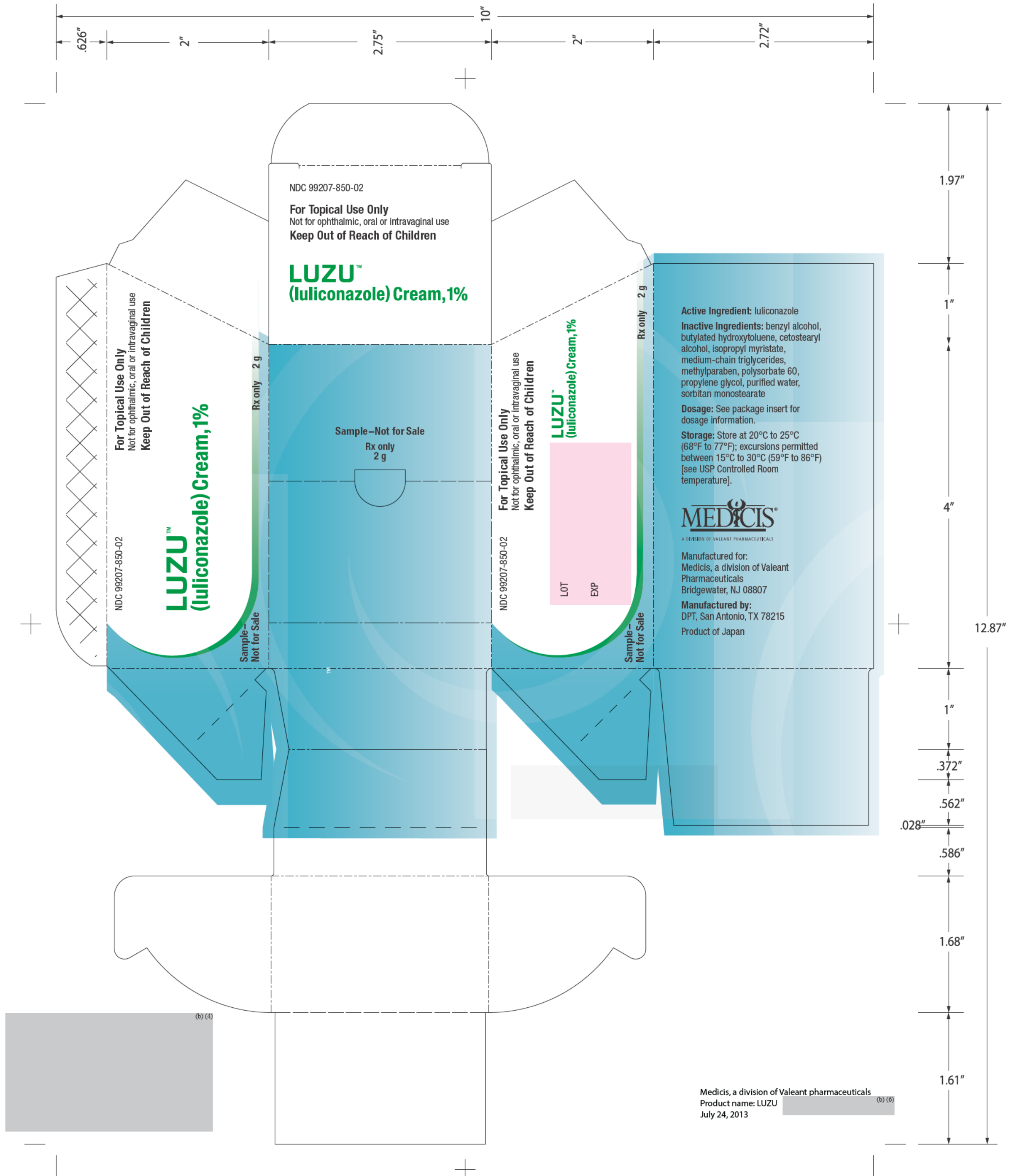
Manufactured by: DPT Laboratories, Ltd., San Antonio, TX 78215

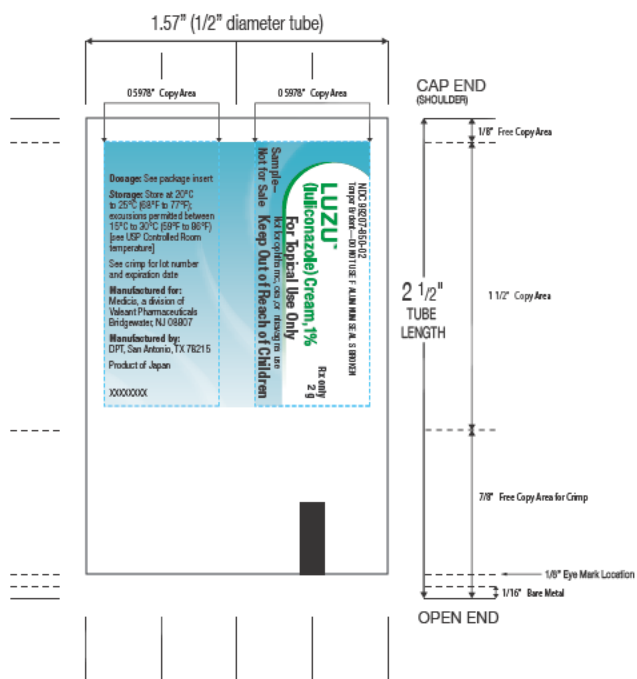
Product of Japan

For more information call 1-800-321-4576.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 11/2013





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NDC 99207-850-60

LUZU™ (Iuliconazole) Cream, 1%

For Topical Use Only
Not for ophthalmic, oral or intravaginal use
Keep Out of Reach of Children

Rx only 60 g

LUZU™
(Iuliconazole) Cream, 1%

LUZU™ (Iuliconazole) Cream, 1%



Manufactured for:
Medicis, a division of Valeant Pharmaceuticals
Bridgewater, NJ 08807

Manufactured by:
DPT, San Antonio, TX 78215
Product of Japan



XXXXXXXX

NDC 99207-850-60

LUZU™ (Iuliconazole) Cream, 1%

For Topical Use Only
Not for ophthalmic, oral or intravaginal use
Keep Out of Reach of Children

Rx only 60 g

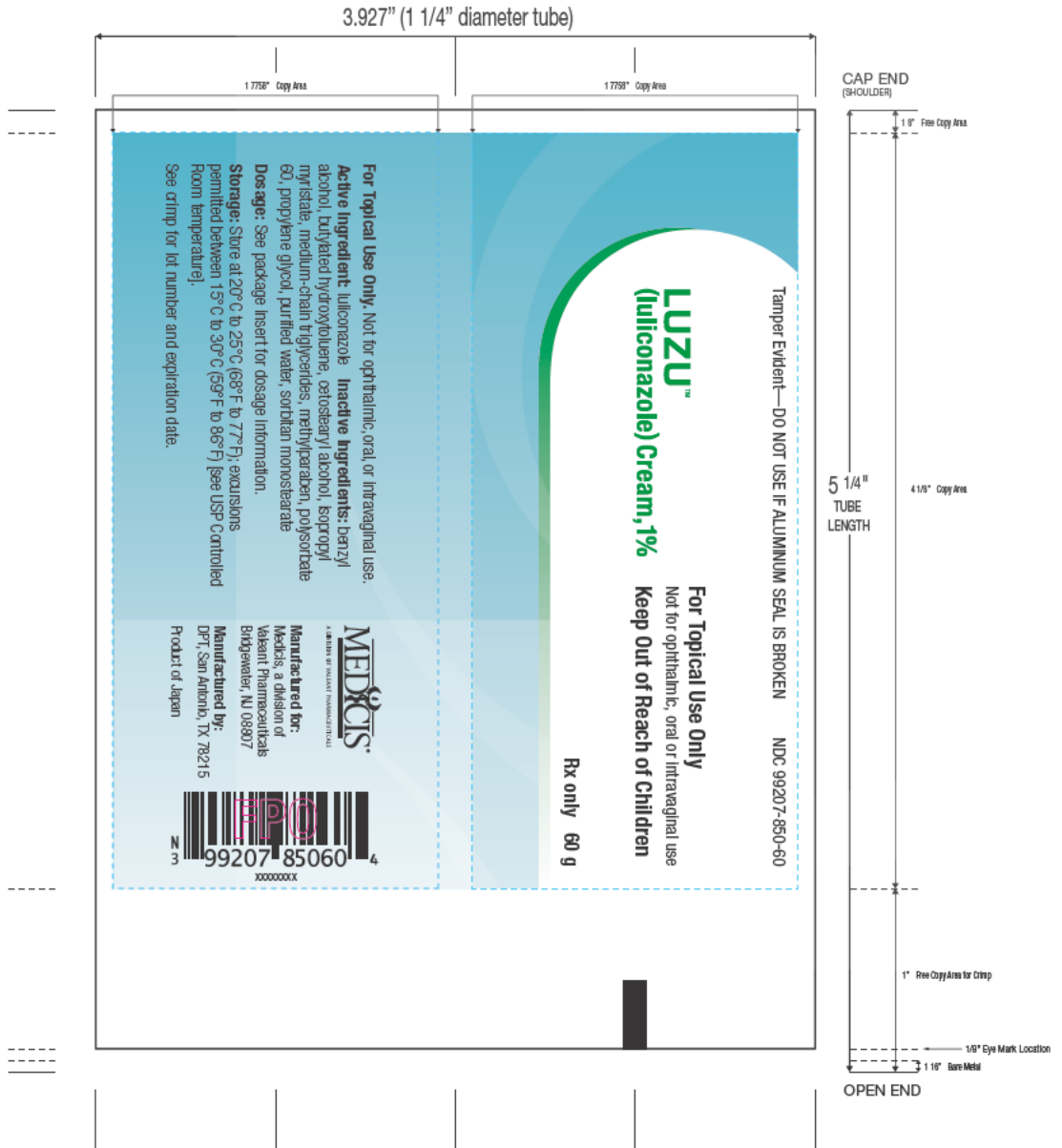
LOT
EXP

Active Ingredient: Iuliconazole **Inactive Ingredients:** benzyl alcohol, butylated hydroxytoluene, cetostearyl alcohol, isopropyl myristate, medium-chain triglycerides, methylparaben, polysorbate 60, propylene glycol, purified water, sorbitan monostearate

Dosage: See package insert for dosage information.

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room temperature].

LUZU™ (Iuliconazole) Cream, 1%



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/s/

JULIE G BEITZ
11/14/2013