SUMMARY OF PRODUCT CHARACTERISTICS FOR LULIZOL CREAM

1. Name of the medicinal product
Trade name: LULIZOL CREAM
Generic name: Luliconazole Cream 1% w/w

2. Qualitative and Quantitative composition
Qualitative Composition

Luliconazole		1 % w/w
Preservative :		
Benzyl Alcohol	BP	1% w/w
Cream base		q.s
For external used only		

3. Pharmaceutical form

Cream
White homogenous semi-solid mass filled in printed lami tubes.

4. Clinical Particulars

Antifungal

ATC No.: D01AC18 Luliconazole

4.1 Therapeutic indications

Luliconazole is indicated for the topical treatment of cutaneous mycosis, i.e tinea ped- is, tinea cruris, and tinea corporis in patients 18 years of age and older.

4.2 Posology and method of administration

For topical use only. Luliconazole is not for ophthalmic, oral, or intravaginal use.

When treating tinea pedis, a thin layer of Luliconazole should be applied to the affected area and approximately 1 inch of the immediate surrounding area(s) once daily for 2 weeks.

When treating tinea cruris or tinea corporis, Luliconazole should be applied to the affected area and approximately 1 inch of the immediate surrounding area(s) once daily for 1 week.

4.3 Contraindications
Luliconazole is contraindicated in patients who have demonstrated hypersensitivity to Luliconazole or any of the inactive ingredients of the formulation.

4.4 Special warnings and precautions for use
Luliconazole is for external use only, avoid contact with eyes. Do not apply to the cornea and conjunctiva as ophthalmic use. Do not apply to the areas with marked erosion/fissures.

4.5 Drug Interactions

An in vivo study in adult subjects with moderate-to-severe interdigital tinea pedis and tinea cruris showed that luliconazole cream, 1%, is a weak inhibitor of CYP2C19.

Results of in vitro studies indicated that therapeutic doses of luliconazole cream, 1%, do not inhibit cytochrome P450 (CYP) enzymes 1A2, 2C9 and 2D6, but can inhibit the activity of CYP2B6, 2C8, 2C19, and 3A4. CYP2C19, the most sensitive enzyme, was further evaluated in an in vivo study using omeprazole as a probe substrate in adult subjects with moderate-to-severe interdigital tinea pedis and tinea cruris. The results showed that luliconazole cream, 1%, applied at a daily amount of approxi- mately 4 grams increased the omeprazole systemic exposure (AUC) by approximate- ly 30% compared to the exposure of omeprazole administered alone.
Luliconazole cream, 1%, is considered a weak inhibitor of CYP2C19.

Results of *in vitro* studies indicated that therapeutic doses of Luliconazole cream,1%, did not induce CYP1A2, 2B6, and 3A4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Luliconazole 1%, in pregnant women. It should be used during pregnancy only if potential benefit justifies the potential risk to the foetus.

Lactation

It is not known whether Luliconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Luliconazole 1% is pre-scribed to women who are breastfeeding.

Pediatric Use

The safety and effectiveness of luliconazole 1% in paediatric patients has not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differ- ences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

4.7 Effects on ability to drive and use machines

There are no any effects shown after using this cream.

4.8 Undesirable effects

Clinical Trial 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the pre-approval clinical studies, incidence of reported adverse reactions was 2.5% (28 cases, 36 events) of the 1,142 patients (1,035 for the cream, 107 for solution). All of the main adverse reactions were localized to the application sites. The data of adverse eventsis presented in the table below.

If the following symptoms occur, appropriate measures, including discontinuation should be taken.

Incidence of adverse events

		≥0.1% to >5%	<0.1 %	Unknown
Cream	Dermatologic	Itching (0.7%), redness (0.6%), irritation (0.5%), contact dermatitis (0.5%), pain (0.4%), and eczema (0.2%)	Hot flush, heat sensation and burning sensation	Vesicle*
	Other		Increase in BUN and increase in urinary protein	
Solution	Dermatologic	Irritation (0.9%) and contact dermatitis (0.9%)		Itching*
*Incidence rate is unknown, due to voluntary report				

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

Post-marketing data

The following adverse reactions have been identified during post marketing use of lu- liconazole cream, 1%: contact dermatitis and cellulitis. Because these reactions are re- ported voluntarily from a population of uncertain size, it is not always possible to reli- ably estimate their frequency or

establish a causal relationship to drug exposure. If you experience any side effects, talk to your doctor or pharmacist or write to drugsafe- ty@cipla.com. You can also report side effects directly via the national pharmacovigi- lance program of India by calling on 1800 180 3024. By reporting side effects you can help provide more information on the safety of this product.

4.9 Overdose

There are no any effects shown after using this cream.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antifungal

ATC Code:

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

5.2 Pharmacokinetic properties

Luliconazole is the R-enantiomer of a chiral molecule. The potential for interconver- sion between R- and Senantiomers in humans has not been assessed. Information on the pharmacokinetics of luliconazole presented below refers to both the 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 sub- jects with moderate-t- -severe tinea cruris applied a mean daily amount of approxi- mately 3.5 grams of luliconazole cream, 1%, to the affected and surrounding areas once daily for 15 days. Plasma concentrations of luliconazole on day 15 were measur- able in all subjects and fluctuated little during the 24-hour interval. In subjects with tinea pedis, the mean ± SD of the maximum concentration (Cmax) was 0.40 ± 0.76 ng/mL after the first dose and 0.93 ± 1.23 ng/mL after the final dose

The mean timeto reach Cmax (Tmax) 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 concen- tration time curve (AUC0–24) 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 ± SD Cmax was 4.91 ± 2.51 ng/mL after the first dose and 7.36 ± 2.66 ng/mL after the final dose. The mean Tmax 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 AUC0– 24, was

85.1 ± 43.69 ng*hr/mL after the first dose and 121.74 ± 53.36 ng*hr/mL after the finaldose.

5.3 Preclinical safety data Carcinogenesis

MutagenesisCarcinogenesis

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).

Reproductive ToxicologyPregnancy & fertility

Fertility

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. Treat- ment-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 reproduc- tive function were noted at 1 mg/kg/day (0.1× MRHD based on BSA comparisons).

Pregnancy

There are no available data with Luliconazole Cream, 1% use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal repro- duction studies with pregnant rats and rabbits, there were no adverse developmental effects observed with subcutaneous administration of luliconazole during organogene- sis at doses up to 3 and 24 times, respectively, the maximum recommended human dose (MRHD)

The background risk of major birth defects and miscarriage for the indicated popula- tion is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

6. Pharmaceutical particulars

6.1 List of Excipients

Disodium Edetate BP
Caprylic Capric Triglyceride BP Isopropyl Myristrate BP
Sepi Neo P 600 IHS
Propylene Glycol BP
Butylated Hydroxytoluene BP Methyl hydroxy benzoate BP Propyl hydroxy benzoate BP
Benzyl Alcohol BP
Transcutol-P IHS
Olivem 1000 IHS
Xanthan gum BP
Perfume Nevia IHS

Purified Water** BP

6.2 Incompatibilities
None known.

6.3 Shelf Life
24 months from the date of manufacturing

Mode of selling
Prescription Only Medicine

6.4 Special Precautions for Storage
Store protected from light & moisture at a temperature not exceeding 30 ^{0}C. Do notfreeze.

6.5 Nature and Contents of container
Pack 20 g semi solid mass in a printed lami tube, with mono carton & printed insert.

6.6 Special precautions for disposal and other handling
Patients should be advised to wash their hands after applying Luliconazole unless it isthe hands that are being treated.

7. Marketing Authorization Holder and Manufacturing site
KLM LABORATORIES PVT. LTD. 1004, Hubtown
Viva, Jogeshwari (E),
Western Express Highway,
Mumbai-400060,
India.

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248011
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8. Marketing Authorization Number
TAN 21 HM 0151

9. Date of First Authorization
29/03/2021

10. Date of Revision of the Text

March 2021