Storage	Store at or below 30℃ in an airtight container away from light and store away from fire
Expiration date	Indicated on the package and container

Therapeutic agent for tinea unguium

LUCONAC®, External Solution for Nails 5% w/w

(Luliconazole Solution)

Contraindication (LUCONAC®, External Solution for Nails 5% w/w is contraindicated in the following patients)

Patients with a past history of hypersensitivity to any of the ingredients of LUCONAC®, External Solution for Nails 5% w/w.

COMPOSITION AND PRODUCT DESCRIPTION

Brand name	LUCONAC®, External Solution for Nails 5% w/w
Active ingredient/ Content (in 1 g)	Luliconazole 50 mg
Inactive ingredients	*N*-methyl-2-pyrrolidone, benzyl alcohol, diisopropyl adipate, lactic acid, povidone, anhydrous ethanol
Product description	A clear and slightly yellowish solution with a characteristic odor

INDICATION

<Susceptible strains>

Dermatophyte (*Trichophyton* spp.)

<Indication>

As topical treatment in adult patients with mild to moderate tinea unguium with symptoms of distal and lateral subungual onychomycosis

<Precautions (Related to Indications)>

1. LUCONAC®, External Solution for Nails 5% w/w should be used in patients with a confirmed diagnosis of tinea unguium based on the results from direct microscopy or culture, etc.
2. The efficacy and safety of LUCONAC®, External Solution for Nails 5% w/w have not been established in severe patients (See "CLINICAL STUDIES").

DOSAGE AND ADMINISTRATION

Apply LUCONAC®, External Solution for Nails 5% w/w once daily to the whole affected nail.

<Precautions (Related to Dosage and Administration)>

Treatment should be continued without interruption until the nail is regenerated and the affected area are finally cured. The required duration of treatment depends essentially on intensity and the localization of the infection and on the growth rate of nails.

LUCONAC®, External Solution for Nails 5% w/w should not be used for a long period of time without a specific reason. Treatment discontinuation and appropriate therapy should be considered if long-term treatment with this product shows no effect.

The safety and efficacy of using LUCONAC®, 5% daily for greater than 48 weeks have not been established.

PRECAUTIONS

1. Adverse Reactions

Out of the 242 subjects who received this product in the Japanese clinical studies, 44 subjects (18.2%) developed adverse reactions. The major adverse reactions were localized to the application site, including dry skin in 13 subjects (5.4%), dermatitis contact in 10 subjects (4.1%), paronychia in 8 subjects (3.3%), eczema in 6 subjects (2.5%), dermatitis, skin irritation, xerosis in 3 subjects each (1.2%), etc. If any of the following symptoms develops, appropriate therapeutic measures such as discontinuation of administration should be taken.

	≥ 1%	0.1 to < 1%	Frequency unknown[Note)]
Dermatologic	Dry skin, dermatitis contact, eczema, dermatitis, skin irritation	Skin exfoliation, erythema, hyperkeratosis	
Others	Paronychia, xerosis	Nail avulsion	Nail discolouration and surrounding skin discolouration

Note) The frequency is unknown because the event was reported spontaneously in Japan.

2. Use During Pregnancy, Delivery, or Lactation

(1) LUCONAC®, External Solution for Nails 5% w/w should be used in women who are or may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established.] See Section *Nonclinical Studies* for toxicity animal reproductive and developmental studies.

(2) LUCONAC®, External Solution for Nails 5% w/w should be used in lactating women only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [Animal studies (subcutaneous administration in rats) have shown that luliconazole is excreted in breast milk[1)]].

3. Pediatric Use

The safety of LUCONAC®, External Solution for Nails 5% w/w in low birth weight infants, neonates, nursing infants, infants or children has not been established (no clinical experience).

4. Precautions concerning Use

Patients should be instructed to pay attention to the followings:

(1) This product is an antifungal drug and does not directly improve discolored nails. Improvement of the affected nail requires eradication of the causative fungus by long-term treatment and growth of new nails (the affected nail is replaced by a normal nail).

(2) Since causative organisms of tinea unguium present in and under the nail plate, LUCONAC®, External Solution for Nails 5% w/w should be fully applied to the whole affected nail, including boundary of the nail. The solution that was applied to the skin around the nail should be wiped off.

(3) Attention should be paid when applying LUCONAC®, External Solution for Nails 5% w/w to the affected nail with wounds around the application site.

(4) When necessary, take care of the affected nail using nail file or nail clippers. Nail files and clippers for affected nails must not be reused on healthy nails.

(5) Cosmetics or artificial nails should not be used on the nail under treatment.

(6) LUCONAC®, External Solution for Nails 5% w/w should be applied only to the nail affected by tinea unguium.

(7) LUCONAC®, External Solution for Nails 5% w/w should not be applied to the cornea or conjunctiva for ophthalmic use.
When you accidentally get LUCONAC®, External Solution for Nails 5% w/w in your eyes, thoroughly flash them with water immediately.

(8) Since LUCONAC®, External Solution for Nails 5% w/w is inflammable, this product should not be used near the fire.

5. Other Precautions

In a study of animals (guinea pig), whose sensitivity was enhanced with adjuvant, skin sensitisation and skin photosensitisation were observed.

PHARMACOKINETICS[2–4)]

(1) When luliconazole was applied to the first toe nails of the 12 Japanese patients with tinea unguium once daily for 5 weeks, the luliconazole concentrations after 5 weeks in the nails were 16,439 ± 9,986 μg/g.

(2) After single application of luliconazole or repeated applications of the drug once daily for 7 days to the total of 20 of fingernails and toenails in 12 Japanese healthy adult volunteers (single application and repeated applications: 6 subjects each), the maximum plasma concentration was 0.10 ± 0.07 ng/mL and 0.14 ± 0.09 ng/mL, respectively.

(3) When luliconazole was applied to the first toe nails (application to other toe nails affected with tinea unguium was allowed, if necessary) once daily for 48 weeks in 194 Japanese patients with tinea unguium, the plasma luliconazole concentrations after 48 weeks were 0.17 ± 0.35 ng/mL.

NON-CLINICAL STUDIES

1. Genotoxicity

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).

2. Carcinogenicity

Non-clinical data reveal no special hazard for humans based on conventional studies of carcinogenic potential including a midterm skin carcinogenicity study in mice and a long-term carcinogenicity study in rats.

3. Reproduction and development toxicity

In reproduction and development toxicity studies in rats exposed to luliconazole via subcutaneous injection, maternal toxicities, reproductive toxicities, embryofetal toxicities and effects on postnatal development were found out at doses ≥5 mg/kg/day. The reproduction and development toxicities were not observed at dose of 1 mg/kg/day which exposure of luliconazole ($AUC_{0\text{-}24h}$: 503 ng·h/mL in males, 983 ng·h/mL in females) was higher than the exposure in repeated administration in humans (2.69 ng·h/mL)[2].

CLINICAL STUDIES

1. Clinical Studies[4]

A randomized, double-blind, parallel-group study examined the efficacy and safety of 48-week once-daily applications of LUCONAC®, External Solution for Nails 5% w/w or a vehicle (placebo) to the first toe nails in 293 Japanese patients with tinea unguium (distal and lateral subungual onychomycosis). The affected area was 20 to 50% of the nail and the height from the nail bed to the surface of the nail plate is to be less than 3 mm. The results of the study were as shown in the table below.

Treatment Group	Complete Cure Rate of Tinea Unguium (# of subjects with cured tinea unguium / # of subjects analyzed)	Fisher's exact test
LUCONAC Group	14.9% (29/194 subjects)	p = 0.012
The placebo Group	5.1% (5/99 subjects)	

Primary endpoint: Complete cure rate after 48 weeks from the start of application (including dropout subjects)

Definition of complete cure rate: The percentage of the subjects in whom affected area completely disappeared (clinical cure) and direct microscopy for Trichophyton was negative (mycological cure).

For reference, the results from the Post-Hoc analysis, which was conducted separately from the primary/secondary endpoints of the clinical study are shown in the table below.

Treatment Group	Complete Cure Rate of Tinea Unguium by Causative Fungus (# of subjects with cured tinea unguium / # of subjects analyzed)	
	Trichophyton rubrum	*Trichophyton mentagrophytes*
LUCONAC Group	4.7% (7/148 subjects)	47.8% (22/46 subjects)
The placebo Group	1.3% (1/76 subjects)	17.4% (4/23 subjects)

2. Skin Irritation[5]

A dermal safety test in 24 Japanese healthy adult volunteers showed neither skin irritation in patch test nor phototoxicity in photopatch test.

PHARMACOLOGY

1. Antifungal effect Non-clinical Studies[6-8]

(1) Antimycotic activity (*in vitro*)

Luliconazole showed antimycotic (MIC) and fungicidal (MCC) activities against *Trichophyton rubrum* and *Trichophyton mentagrophytes*, major causative fungi of tinea unguium.

Strain	MIC_{90} and MCC_{90} (μg/mL)
T. rubrum	
MIC_{90} (59 strains)	0.0010
MCC_{90} (10 strains)	0.0050
T. mentagrophytes	
MIC_{90} (26 strains)	0.0010
MCC_{90} (10 strains)	0.010

(2) A drug effect test using human tinea unguium model (*in vitro*)

After the bottom side of the clipped human nail plate was infected with *T. mentagrophytes*, when LUCONAC® Solution 5% was repeatedly applied to the top side of the nail plate once daily for 7 days, decrease in the volume of ATP derived from the fungus bodies was observed.

2. Mechanism of Action[9]

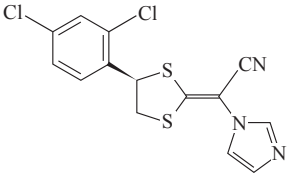
Luliconazole shows antifungal effect by inhibiting synthesis of ergosterol, a component of the cell membrane of a fungus

PHYSICOCHEMICAL PROPERTIES

Nonproprietary name: Luliconazole (JAN, INN)

Chemical name: (-)-(*E*)-[(4*R*)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene](1*H*-imidazol-1-yl) acetonitrile

Structural formula:



Molecular formula: $C_{14}H_9Cl_2N_3S_2$

Molecular weight: 354.28

Description: Luliconazole occurs as pale yellow to light yellow crystal or crystalline powder. It is freely soluble in *N*,*N*-dimethylformamide or acetone, soluble in acetonitrile or methanol, sparingly soluble in ethanol (99.5), and is practically insoluble to water. It is slowly colored by light.

Melting point: 150-153°C

PRECAUTIONS FOR HANDLING

(1) Tighten the cap after opening it and store it.
(2) Store this product out of the reach of children.
(3) Pay attention since this product may cause yellowing of your clothes.
(4) Pay attention since this product may cause softening of synthetic resin and dissolving of paint.
(5) Since this product is inflammable, use or store it away from fire.
(Strict prohibition of fire, Class I petroleum, Hazardous Rank II)

PACKAGING

3.5 g (4 mL) × 1, 10
(polypropylene vessel, with LDPE inner closure and polypropylene cap)

REFERENCES

1) In-house data of Sato Pharmaceutical Co., Ltd.: Pharmacokinetic Study
2) In-house data of Sato Pharmaceutical Co., Ltd.: Clinical Pharmacology Study
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4) In-house data of Sato Pharmaceutical Co., Ltd.: Phase III Clinical Study
5) In-house data of Sato Pharmaceutical Co., Ltd.: Phase I Clinical Study (Dermal Safety)
6) In-house data of Sato Pharmaceutical Co., Ltd.: Pharmacological Study [1]
7) Koga, H. et al.: J. Infect. Chemother., 12, 163-165 (2006)
8) Shimamura, T. et al.: Med. Mycol., 57, J13-J18 (2016)
9) Niwano, Y. et al.: Med. Mycol., 37, 351-355 (1999)

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