Summary Report of Benefit-Risk Assessment

LUCONAC EXTERNAL SOLUTION FOR NAILS 5%

NEW DRUG APPLICATION

Active Ingredient(s)	Luliconazole
Product Registrant	Zuellig Pharma Pte Ltd
Product Registration Number	SIN16428P
Application Route	Abridged Evaluation
Date of Approval	14 February 2022

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A INTRODUCTION

Luconac is indicated as a topical treatment in adult patients with mild to moderate tinea unguium with symptoms of distal and lateral subungual onychomycosis caused by *Trichophyton* spp.

The active substance, luliconazole, is an antifungal that inhibits biosynthesis of ergosterol, a component of the cell membrane of *Trichophyton rubrum* and *Trichophyton mentagrophytes,* major causative fungi of tinea unguium.

Luconac is available as a solution for external application containing 50mg/g of luliconazole. Other ingredients in the solution are *N*-methyl-2-pyrrolidone, benzyl alcohol, diisopropyl adipate, lactic acid, povidone and anhydrous ethanol.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, luliconazole, is manufactured at [redacted]. The drug product, Luconac External Solution for Nails 5%, is manufactured at Sato Pharmaceutical Co., Ltd., Chiba, Japan.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for [redacted] was adequate to support the storage at room temperature (1°C - 30°C) with a re-test period of 60 months. The packaging is a transparent polyethylene bag placed into a black outer polyethylene bag. These bags are then placed into a fibre drum.

Drug product:

The solution is manufactured by mixing the drug substance with excipients, followed by filling of the solution into the vessels. The process is considered to be a standard process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and the impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a polypropylene vessel with low density polyethylene inner closure and a polypropylene cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of luliconazole in the treatment of tinea unguium with mild to moderate symptoms of distal and lateral subungual onychomycosis was based on data from one pivotal phase II/III study SKN-08-01.

Study SKN-08-01 was a multicentre, randomised, placebo-controlled, double-blind, parallel-group study conducted in adult patients with tinea unguium having mild to moderate symptoms of distal and lateral subungual onychomycosis. The subjects were randomised in a 2:1 ratio to receive once-daily application of either luliconazole 5% solution or placebo for 48 weeks. The study duration of 48 weeks was considered appropriate considering the rate of growth of new toenail to replace the affected toenail. Patients returned to the study centre 4 weeks later for a post-observation visit to examine recurrence of the infection.

The primary endpoint was cure rate for tinea unguium in the affected nail at Week 48. Tinea unguium of the nail plate under investigation is considered cured if the opaque area in the nail plate disappeared and there was no dermatophyte element under direct microscopy.–The secondary endpoints were only exploratory in nature, including the recurrence of tinea unguium, defined as presence of tinea unguium opaque area in the nail plate and direct microscopic evidence of dermatophyte element after the 4-week post-observation period in patients who were judged cured at Week 48. Other secondary endpoints included the rate of increase in the healthy area of the affected nail plate and proportion of patients without evidence of *Trichophyton* by direct microscopy and loop-mediated isothermal amplification (LAMP).

A total of 293 adult patients (luliconazole: 194; placebo: 99) were randomised and received the study drug. These patients formed the Full Analysis Set (FAS) for the primary efficacy analysis. The supportive efficacy analyses were performed for the Per Protocol Set (PPS) (luliconazole: 180; placebo: 96) which excluded 17 patients from the FAS due to protocol deviations related to the use of prohibited concomitant drugs and non-compliance during observation period of the investigational. The demographic and baseline characteristics were generally balanced between the treatment arms. The mean age of the patients was 57.6 years (range: 21 to 60 years). On average, the study toenail had 37.4 % (range: 19.9 % to 50.5 %) opaque area due to the infection and 76.5% of the infections were due to *Trichophyton rubrum*.

Treatment with luliconazole resulted in a statistically higher cure rate after 48 weeks compared to placebo. The cure rate for tinea unguium in the affected nail was 14.9% (29/194 patients) in the luliconazole group compared to 5.1% (5/99) in the placebo group (p=0.012). The results from the PPS showed similar results to the primary analysis (p=0.011). Subgroup analyses by the type of dermatophytes (*T. rubrum* and *T. mentagrophytes*), proportion of the nail

involvement and height from the nail bed showed that cure rates were in favour of luliconazole compared to placebo.

The results of the secondary endpoints were generally consistent with those from the primary analysis. At Week 48, patients treated with luliconazole had a greater rate of increase in the proportion of healthy area in the affected nail plate compared to placebo (luliconazole: 14.07%; placebo: 0.77%; p=0.003). A greater proportion of patients in the luliconazole group was tested negative for *Trichophyton* compared to placebo based on direct microscopy (45.4% vs 31.2%, respectively; p=0.026) and LAMP (56.9% vs 36.6%, respectively; p=0.002). Among the patients who achieved cure at Week 48, none had recurrence of the disease 4 weeks later.

Summary of Key Efficacy Results (Study SKN-08-01) (FAS)

Endpoint	Luliconazole (N=194)	Placebo (N=99)
Primary endpoint – Cure rate at Week 48		
n (%)	29 (14.9)	5 (5.1)
p-value (Fisher's exact test)	0.012	
Secondary endpoint – Rate of Increase in Proportion of Healthy Area at Week 48		
Mean ± SD (%)	14.07 ± 35.486	0.77 ± 31.846
Range (Min, Max)	(-87.6, 98.3)	(-84.6, 63.2)
p-value (Student's t-test)	0.003	
Secondary endpoint – Negative presence of dermatophyte (direct microscopy) at Week 48		
n/N (%)	79/174 (45.4)	29/93 (31.2)
p-value (Fisher's exact test)	0.026	
Secondary endpoint – Negative presence of Trichophyton (LAMP) at Week 48		
n/N (%)	99/174 (56.9)	34/93 (36.6)
p-value (Fisher's exact test)	0.002	
Secondary endpoint – Recurrence rate after post-study observation period		
n (%)	0	0
p-value	-	

Overall, Study SKN-08-01 demonstrated efficacy of luliconazole for the treatment of patients with tinea unguium having mild to moderate symptoms of distal and lateral subungual onychomycosis.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of luliconazole was based on the safety data from Study SKN-08-01 comprising a total of 293 subjects who received at least one dose of study treatment (luliconazole: 194; placebo: 99). The median duration of exposure was similar in both treatment groups (luliconazole: 336 days; placebo: 335 days).

Overview of Safety Profile (Study SKN-08-01)

AE n (%)	Luliconazole (N=194)	Placebo (N=99)
Any AE	152 (78.4)	76 (76.8)
Treatment-related AE	44 (22.7)	4 (4.0)
SAE	7 (3.6)	8 (8.1)
Treatment-related SAE	0	0
Discontinuations due to AE	12 (6.2)	2 (2.0)
Deaths due to AE	0	0

AE: adverse event; SAE: serious adverse event

The incidences of any adverse events (AEs) were similar between luliconazole and placebo. The most commonly reported AEs in luliconazole group (incidence of 5% or higher) were nasopharyngitis (luliconazole vs placebo: 22.2% vs 24.2%), eczema (13.4% vs 13.1%), contact dermatitis (7.7% vs 5.1%]), dry skin (7.2% vs 2.0%), hyperkeratosis (7.2% vs 5.1%), seasonal allergy (6.7% vs 4.0%) and traumatic haematoma (5.2% vs 8.1%). Incidences of contact dermatitis, dry skin and hyperkeratosis were slightly higher in the luliconazole group than the placebo control. The most common treatment-related topical AEs were dermatitis contact and dry skin. None of the topical AEs were serious AEs (SAEs). The 7 SAEs reported in the luliconazole group were cataract in 2 subjects and cerebral infarction, diverticulitis, colitis ulcerative, meniscus injury, and haematuria each in 1 subject but none was related to luliconazole.

There were 12 patients (6.2 %) in the luliconazole arm and 2 patients (2.0 %) in the placebo arm who experienced AEs that led to discontinuation of the treatment. Most of these AEs were assessed by the investigator to be “resolved” or “resolving”, indicating the reversibility of the events with treatment discontinuation.

Overall, topical luliconazole 5% was well tolerated and presented an acceptable safety profile for the intended patient population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Tinea unguium is an infection of the nail caused by dermatophytes with *Trichophyton mentagrophytes* and *Trichophyton rubrum* being the most common causative agents. Oral antifungal therapy is considered the gold standard for onychomycosis because of shorter courses of treatment and higher cure rates when compared with topical antifungal therapy. However, topical drug therapy presents an alternative option in patients who are unable to tolerate oral antifungal therapy.

The study demonstrated superiority of luliconazole 5% solution over placebo for the treatment of tinea unguium in patients with mild to moderate symptoms of distal and lateral subungual onychomycosis. Clinical cure was achieved in 14.9% of the subjects in the luliconazole group compared to 5.1% of the subjects in the placebo group after 48 weeks of treatment, and none of the cured subjects experienced recurrence of the disease after stopping the treatment. Among subjects who did not achieve the defined cure of the disease, improvement in terms of the increase in the area of the healthy nail plate and a larger proportion of the patients tested negative for *Trichophyton* were observed in the luliconazole treated subjects compared to the placebo.

The safety profile of luliconazole was considered acceptable. Most adverse events were mild to moderate in severity and the topical AEs were reversible with discontinuation of treatment.

Overall, the benefits of luliconazole 5% in the treatment of mild to moderate tinea unguium and symptoms of distal and lateral subungual onychomycosis outweighed the risks associated with treatment.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of luliconazole 5% for the topical treatment in adult patients with mild to moderate tinea unguium with symptoms of distal and lateral subungual onychomycosis was deemed favourable and approval was granted on 14 February 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

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 *Non-clinical 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 mid-term 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]

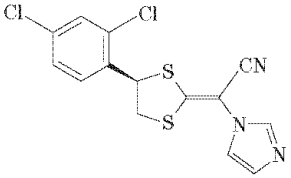
Luliconazole shows antifungal effect by inhibiting synthesis of ergosterol, a component of the cell membrane of a fungus

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) × 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
3) In-house data of Sato Pharmaceutical Co., Ltd.: Phase I Clinical Study (Pharmacokinetics)
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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