Summary Report of Benefit-Risk Assessment

WINLEVI CREAM 1% w/w

NEW DRUG APPLICATION

Active Ingredient(s)	Clascoterone
Product Registrant	Hyphens Pharma Pte. Ltd.
Product Registration Number	SIN17072P
Application Route	Abridged evaluation
Date of Approval	28 August 2024

Copyright © 2025 Health Sciences Authority of Singapore

You may download, view, print and reproduce this summary report without modifications for non-commercial purposes only. Except as otherwise provided, the contents of this summary report may not be reproduced, republished, uploaded, posted, transmitted or otherwise distributed in any way without the prior written permission of the Health Sciences Authority.

This summary report and its contents are made available on an “as is” basis and the Health Sciences Authority makes no warranty of any kind, whether express or implied.

The information in the summary report is provided for general information only and the contents of the summary report do not constitute medical or other professional advice. If medical or other professional advice is required, services of a competent professional should be sought.

Table of Contents

A INTRODUCTION 3
B ASSESSMENT OF PRODUCT QUALITY 3
C ASSESSMENT OF CLINICAL EFFICACY 4
D ASSESSMENT OF CLINICAL SAFETY 6
E ASSESSMENT OF BENEFIT-RISK PROFILE 7
F CONCLUSION 7

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

A INTRODUCTION

Winlevi 1% w/w Cream is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

The active substance, clascoterone, is an androgen receptor inhibitor. The mechanism of action of clascoterone for the topical treatment of acne vulgaris is unknown. It has a chemical structure similar to dihydrotestosterone and competes with the natural substrate for binding to androgen receptors in the skin.

Winlevi is a white to almost white cream that contains 1% w/w clascoterone. Other ingredients in the cream are cetyl alcohol, mono- and di-glycerides, mineral oil, propylene glycol, vitamin E, edetate disodium, polysorbate 80, citric acid monohydrate and purified water.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, clascoterone, is manufactured at [redacted]
The drug product, Winlevi, is manufactured at Cosmo S.p.A., Lainate, Milan, Italy.

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 has been performed in accordance with ICH guidelines. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the approved storage condition [redacted] and re-test [redacted]. The packaging consists [redacted]

Drug product:

The cream manufacturing [redacted] is considered a standard process.

The manufacturing site is compliant with Good Manufacturing Practice. 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.

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

The specifications were established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at 2°C to 8°C. After first opening, the drug product should be stored at or below 30°C, away from direct sunlight and heat, and the unused portion discarded one month after first opening. The container closure system is an epoxy lined aluminium, blind-end tube, with a polypropylene cap containing 60, 30, 10 or 2 grams of cream.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy and safety of Winlevi cream 1% in the treatment of acne vulgaris was based on two identically designed Phase 3, multicentre, randomised, double-blind, vehicle-controlled trials (Studies 25 and 26), which comprised 1,440 patients aged 9 years or older with moderate to severe facial acne vulgaris.

Eligible subjects were randomised in a 1:1 ratio to Winlevi or vehicle cream. Subjects applied the assigned study drug to the entire face twice daily (BID) for 12 weeks. Subjects who completed the treatment phase of this study could participate in the open-label, long-term follow-up study (Study 27), where all subjects, regardless of the treatment used in the double-blind study, applied Winlevi cream 1% BID on the face and, if applicable, the trunk for up to 9 additional months of treatment.

The three co-primary endpoints in hierarchical order were: proportion of subjects in each treatment group with Investigator's Global Assessment (IGA) success, defined as at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 (clear) or 1 (almost clear) at Week 12; absolute change from baseline in non-inflammatory lesion count (NILC) at Week 12; and absolute change from baseline in inflammatory lesion count (ILC) at Week 12. The secondary endpoints were absolute change from baseline in total lesion count (TLC), and percent change from baseline in TLC, NILC and ILC at Week 12.

In Study 25, a total of 708 subjects were randomised, with 353 subjects allocated to the Winlevi treatment arm and 355 subjects to the vehicle arm. The majority of subjects were female (61.6%) and white (84.0%), with a mean age of 19.9 years (ranging from 9 to 58). Most subjects had acne vulgaris of moderate severity, with 82.7% in the Winlevi group and 82.0% in the vehicle group.

In Study 26, 732 subjects were randomised, with 369 subjects assigned to the Winlevi arm and 363 to the vehicle arm. The majority of subjects were female (63.4%) and white (96.3%), with a mean age of 19.2 years (ranging from 10 to 50). Similarly, most subjects had acne vulgaris of moderate severity, with 82.7% in the Winlevi group and 86.2% in the vehicle group. The baseline characteristics and demographics were generally well balanced between the treatment arms across the two studies.

The co-primary endpoints were met in both pivotal studies. In Study 25, a statistically significantly greater proportion of subjects treated with Winlevi achieved IGA "success" compared to subjects treated with vehicle (18.8% vs 8.9%, p = 0.0008) at Week 12. The

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

absolute change from baseline to Week 12 in the Winlevi group was statistically significantly greater than the vehicle group for both NILC (-19.4 vs -13.1, p = 0.0016) and ILC (-19.4 vs -15.5, p = 0.0029). In Study 26, a statistically significantly greater proportion of subjects treated with Winlevi achieved IGA "success" compared to subjects treated with vehicle (20.8% vs 6.5%, p < 0.0001) at Week 12. The absolute change from baseline to Week 12 in the Winlevi group was statistically significantly greater than the vehicle group for both NILC (-19.4 vs -10.9, p < 0.0001) and ILC (-20.0 vs -12.6, p < 0.0001). Winlevi also demonstrated consistent improvements compared to vehicle across the secondary endpoints.

Summary of efficacy results (Studies 25 and 26)

	Study 25		**Study 26**	
	Winlevi (N = 353)	**Vehicle (N = 355)**	**Winlevi (N = 369)**	**Vehicle (N = 363)**
Primary endpoints				
IGA success at Week 12 (%)	18.8	8.9	20.8	6.5
Difference (95% CI) p-value	9.9 (4.0, 15.7) p = 0.0008		14.3 (8.9, 19.7) p < 0.0001	
Absolute change from baseline in NILC at Week 12	-19.4	-13.1	-19.4	-10.9
Difference (95% CI) p-value	-6.3 (-10.2, -2.4) p = 0.0016		-8.4 (-12.4, -4.5) p < 0.0001	
Absolute change from baseline in ILC at Week 12	-19.4	-15.5	-20.0	-12.6
Difference (95% CI) p-value	-3.9 (-6.5, -1.3) p = 0.0029		-7.4 (-9.8, -5.0) p < 0.0001	
Secondary endpoints				
Absolute change from baseline in TLC at Week 12	-39.2	-28.9	-40.3	-23.7
Difference (95% CI) p-value	-10.3 (-15.7, -5.0) p = 0.0002		-16.6 (-22.0, -11.1) p < 0.0001	
Percent change from baseline in TLC at Week 12 (%)	-37.1	-28.5	-37.7	-22.2
Difference (95% CI) p-value	-8.7 (-14.0, -3.3) p = 0.0016		-15.6 (-20.9, -10.3) p < 0.0001	
Percent change from baseline in NILC at Week 12 (%)	-30.7	-21.9	-29.3	-15.8
Difference (95% CI) p-value	-8.8 (-15.9, -1.8) p = 0.0141		-13.5 (-19.8, -7.1) p < 0.0001	
Percent change from baseline in ILC at Week 12 (%)	-44.8	-36.6	-47.0	-29.8
Difference (95% CI) p-value	-8.3 (-14.3, -2.3) p = 0.0070		-17.2 (-22.9, -11.5) p < 0.0001	

IGA: Investigator's Global Assessment; ILC: Inflammatory lesion count; NILC: Non-inflammatory lesion count; TLC: Total lesion count

In the subgroup analyses stratified by age, consistent treatment benefits in terms of IGA success were demonstrated in both the 12 to <18 years (n = 641; 15.8% vs 4.3%; p < 0.0001) and 18 to <65 years (n = 780; 21.3% vs 10.0%; p < 0.0001) subgroups. However, in subjects 9 to <12 years of age (n = 19), there was no observed benefit with respect to IGA success at Week 12(15.4% in the Winlevi arm vs 18.0% in the vehicle arm; p = 0.9071). Data in this

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

subgroup of patients was limited due to the small sample size, and the clinical studies results failed to demonstrate efficacy.

In the long-term Study 27, among the subjects who were on-study for the maximum period (12 months for the face and 9 months for the trunk), an IGA score of clear or almost clear was reported for facial acne for 56% of 123 subjects and truncal acne for 59% of 49 subjects, demonstrating maintenance of efficacy.

Overall, the efficacy of Winlevi cream 1% for the treatment of acne vulgaris in patients 12 years and older has been demonstrated based on statistically significant and clinically relevant improvement in the proportion of subjects who achieved IGA success and absolute and percent changes from baseline in NILC, ILC and TLC.

D ASSESSMENT OF CLINICAL SAFETY

The safety population comprised a total of 1,440 subjects (722 subjects in the Winlevi group and 718 in the vehicle group) enrolled in Studies 25 and 26 for a duration of exposure of up to 12 weeks, and supported by long-term safety data from Study 27 of up to 12 months.

Summary of treatment-emergent adverse events (TEAEs) in Studies 25 and 26

Category, n (%)	Winlevi (N = 722)	Vehicle (N = 718)
All TEAEs	82 (11.4)	91 (12.7)
Related TEAE	12 (1.7)	22 (3.1)
SAE	0	2 (0.3)
TEAE leading to treatment discontinuation	5 (0.7)	12 (1.7)
TEAE leading to death	0	0

In the pooled Phase 3 studies, local skin reactions such as oedema, erythema/redness, pruritus, scaling/dryness, skin atrophy, stinging/burning, striae rubrae, and telangiectasia occurred at similar rates between Winlevi and vehicle. The most frequent treatment-emergent local skin reactions were erythema (12.2% Winlevi vs 15.3% vehicle) and scaling/dryness (10.5% Winlevi vs 10.3% vehicle). Most of the local skin reaction AEs were trace or mild in severity. No serious adverse events (SAEs) occurred in the Winlevi arm, whereas 2 SAEs were reported in the vehicle arm. Additionally, no deaths were reported in either treatment arm. The safety profile of Winlevi with long-term exposure of up to 12 months was generally consistent with that observed in the 12-week Phase 3 studies.

Hypothalamic-pituitary-adrenal (HPA) axis suppression was an adverse event of special interest (AESI). In a maximal use Study 202, HPA axis suppression indicated by 30-minute post-stimulation serum cortisol level of ≤18 mcg/dL was observed in 1 out of 20 (5%) adult subjects and 2 out of 22 (9%) adolescent subjects at Day 14. All subjects returned to normal HPA axis function at follow-up 4 weeks after the end of treatment. AEs related to HPA axis suppression were not reported in the clinical studies. Nonetheless, warnings and precautions on HPA axis suppression have been included in the product labelling.

Overall, Winlevi was generally well tolerated with a safety profile comparable to that of the vehicle. Appropriate warnings and dose modification recommendations are included in the

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

product labelling to mitigate the known risks including local skin reactions and HPA axis suppression.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Acne vulgaris is a common chronic disease that may be associated with impairment of quality of life. Winlevi provides an additional option to current available topical and systemic treatments such as retinoids and antibiotics for patients with moderate to severe acne.

In the Phase 3 placebo-controlled Studies 25 and 26, statistically significant and clinically meaningful improvements were demonstrated for Winlevi compared to placebo in terms of IGA success, absolute change in NILC, and absolute change in ILC over a duration of 12 weeks. Results from the long-term Study 27 showed that the efficacy of Winlevi was maintained for up to 12 months.

Winlevi was generally well tolerated, with a safety profile comparable to that of vehicle in both the pivotal and long-term studies. Relevant warnings regarding local skin reactions, including erythema and scaling/dryness, as well as HPA axis suppression have been included in the product labelling.

Overall, the benefits of Winlevi in the treatment of acne for patients 12 years and above outweigh the known risks.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk of Winlevi for the treatment of acne vulgaris was considered favourable and approval of the product registration was granted on 28 August 2024.

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

APPROVED PACKAGE INSERT AT REGISTRATION

Health Products Regulation Group • Blood Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

1 NAME OF THE MEDICINAL PRODUCT
WINLEVI (Clascoterone) cream 1%

2 INDICATIONS AND USAGE
WINLEVI (clascoterone) cream is an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

3 DOSAGE AND ADMINISTRATION
Cleanse the affected area gently. After the skin is dry, apply a thin uniform layer of WINLEVI cream twice per day, in the morning and the evening, to the affected area. Avoid accidental transfer of WINLEVI cream into eyes, mouth or other mucous membranes. If contact with mucous membranes occurs, rinse thoroughly with water.

WINLEVI cream is for topical use only. WINLEVI cream is not for ophthalmic, oral or vaginal use.

4 DOSAGE FORMS AND STRENGTHS
Cream 1%. Each gram of WINLEVI cream contains 10 mg of clascoterone in a white to almost white cream.

5 CONTRAINDICATIONS
None.

6 WARNINGS AND PRECAUTIONS
6.1 Local Skin Reactions
WINLEVI cream may induce local irritation (erythema/redness, pruritus, scaling/ dryness). Concomitant use with other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices or lime) should be limited.

The product should not be applied to cuts, abrasions, eczematous or sunburned skin.

6.2 Hypothalamic-pituitary-adrenal (HPA) Axis Suppression
Hypothalamic-pituitary-adrenal (HPA) axis suppression was observed and may occur during or after treatment with clascoterone. In the PK trial, all subjects returned to normal HPA axis function at follow-up 4 weeks after stopping treatment [see Clinical Pharmacology (10.2)]. Conditions which augment systemic absorption include use over large surface areas, prolonged use, and the use of occlusive dressings.

If HPA axis suppression develops, an attempt should be made to withdraw the drug.

Pediatric patients may be more susceptible to systemic toxicity.

7 ADVERSE REACTIONS
7.1 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 two identical multicenter, randomized, double-blind, vehicle-controlled trials, 1421 subjects 12 years and older with facial acne vulgaris applied WINLEVI cream or vehicle twice daily for 12

weeks. Overall, 62% of the subjects were female, and 38% were male, 91% of the patients were Caucasian, and the mean age was 19.7 years.

Local skin reactions (edema, erythema/redness, pruritus, scaling/dryness, skin atrophy, stinging/burning, striae rubrea, telangiectasia) were observed during the12-week treatment and occurred in a similar percentage of subjects treated with vehicle. Local skin reactions reported by ≥ 1% of subjects treated with WINLEVI cream are shown in the following table.

Table 1. Incidence of New or Worsening Local Skin Reactions Reported by ≥ 1% of Subjects Treated with WINLEVI Cream After Day 1 in 12-Week Controlled Clinical Trials

	WINLEVI Cream 1% (N=674[a])	**Vehicle Cream (N=656[a])**
Edema	24 (3.6%)	23 (3.5%)
Erythema/redness	82 (12.2%)	101 (15.4%)
Pruritus	52 (7.7%)	54 (8.2%)
Scaling/dryness	71 (10.5%)	68 (10.4%)
Skin atrophy	11 (1.6%)	17 (2.6%)
Stinging/burning	28 (4.2%)	28 (4.3%)
Striae rubrae	17 (2.5%)	10 (1.5%)
Telangiectasia	8 (1.2%)	12 (1.8%)

[a] The denominators for calculating the percentages were the 674 of 709 subjects treated with WINLEVI cream and 656 of 712 subjects treated with vehicle in these trials who had local skin reaction results reported after Day 1.

The following adverse reactions associated with the use of WINLEVI cream were identified in clinical trials and long-term safety studies.

Metabolism: hyperkalemia [see Clinical Pharmacology (10.2)]

Reproductive: polycystic ovaries, amenorrhea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on WINLEVI cream use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, subcutaneous administration of clascoterone to pregnant rats and rabbits during organogenesis at doses 8 or 39 times the maximum recommended human dose (MRHD), respectively, increased malformations in rats and post-implantation loss and resorptions in rabbits *(see Data).*

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. 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.

Data

Animal Data

In an embryofetal development study, clascoterone was administered subcutaneously to pregnant rats at doses of 1, 5, or 25 mg/kg/day during the period of organogenesis. No clascoterone-related maternal toxicity or effects on uterine parameters were noted at doses up

to 25 mg/kg/day (336 times the MRHD based on AUC comparison). Clascoterone-related malformations were noted at all dose levels, without a dose relationship. Omphalocele was noted in a single fetus at each dose level. External and visceral malformations (severe dilation of the lateral and third cerebral ventricles; thin skin, small size, and protruding tongue) were noted in two additional fetuses at 1 mg/kg/day (8 times the MRHD based on AUC comparison).

In an embryofetal development study, clascoterone was administered subcutaneously to pregnant rabbits at doses of 0.1, 0.4, or 1.5 mg/kg/day during the period of organogenesis. Post-implantation loss and resorptions were increased at 1.5 mg/kg/day (39 times the MRHD based on AUC comparison). No developmental toxicity was noted at doses up to 0.4 mg/kg/day (12 times the MRHD based on AUC comparison). No clascoterone-related maternal toxicity or fetal malformations were noted at doses up to 1.5 mg/kg/day (39 times the MRHD based on AUC comparison).

In a prenatal and postnatal development study, clascoterone was administered subcutaneously to pregnant rats at doses of 0.5, 2.5, and 12.5 mg/kg/day beginning on gestation day 6 and continuing through lactation day 20. No significant maternal or developmental toxicity was observed at doses up to 12.5 mg/kg/day (163 times the MRHD based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data regarding the presence of clascoterone or metabolite in human milk, the effects on the breastfed infant or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of clascoterone to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clascoterone and any potential adverse effects on the breastfed child from clascoterone or from the underlying maternal condition.

8.3 Pediatric Use

Safety and effectiveness of WINLEVI cream for the topical treatment of acne vulgaris have been established in 641 pediatric patients, aged 12 to 18 years in two identical multicenter, randomized, double-blind, vehicle-controlled, 12-week trials and 2 open-label pharmacokinetic studies. *[see Clinical Studies (12)].*

Safety and effectiveness of WINLEVI cream for the topical treatment of acne vulgaris has not been established in pediatric patients under 12 years of age.

Hypothalamic-pituitary-adrenal (HPA) axis suppression was observed in 2/22 (9%) adolescent subjects. All subjects returned to normal HPA axis function at follow-up 4 weeks after stopping the treatment *[see Clinical Pharmacology (10.2)].* Children may be more susceptible to systemic toxicity when treated with clascoterone. *[see Pharmacodynamics (10.2)].*

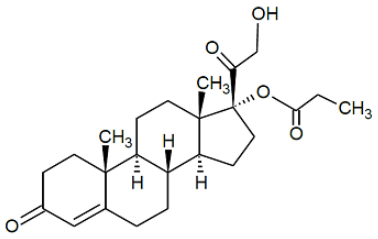
8.4 Geriatric Use

Clinical studies of WINLEVI cream did not include sufficient numbers of subjects aged 65 years of age and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

9 DESCRIPTION

WINLEVI (clascoterone) cream contains clascoterone, an androgen receptor inhibitor, in a cream base for topical dermatologic use. WINLEVI cream is a white to almost white cream.

Chemically, clascoterone is cortexolone-17α propionate. Clascoterone is a white to almost white powder, practically insoluble in water. The compound has the empirical formula $C_{24}H_{34}O_5$ and molecular weight of 402.5 g/mol. The structural formula is shown below.



Each gram of WINLEVI cream 1% contains 10 mg of clascoterone in a cream base of cetyl alcohol, citric acid monohydrate, edetate disodium, mineral oil, mono- and di-glycerides, polysorbate 80, propylene glycol, purified water, and vitamin E.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Clascoterone is an androgen receptor inhibitor. The mechanism of action of WINLEVI cream for the topical treatment of acne vulgaris is unknown.

10.2 Pharmacodynamics

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

HPA axis suppression was evaluated in adult (n=20) and adolescent (n=22) subjects with acne vulgaris following twice daily application of WINLEVI cream for 2 weeks in the pharmacokinetic study described in Section 12.3. HPA axis suppression indicated by 30-minute post-stimulation serum cortisol level of ≤18 mcg/dL was observed in 1/20 (5%) of adult subjects and 2/22 (9%) of adolescent subjects at Day 14. All subjects returned to normal HPA axis function at follow-up 4 weeks after the end of treatment.

Potassium

Shifts from normal to elevated potassium levels were observed in 5% of clascoterone-treated subjects and 4% of vehicle-treated subjects.

Cardiac Electrophysiology

At approximately 2-times the systemic exposure observed with the maximum dose, WINLEVI cream does not prolong the QT interval to any clinically relevant extent.

10.3 Pharmacokinetics

Absorption

Following topical treatment of WINLEVI cream for 2 weeks with a mean dose of approximately 6 grams applied twice daily to adult subjects with moderate to severe acne vulgaris (n=20), systemic concentrations of clascoterone were at steady state by Day 5. On Day 14, the mean ± SD maximum plasma concentration (C_{max}) was 4.5 ± 2.9 ng/mL, the mean ± SD area under the plasma concentration-time over the dosing interval (AUC_{τ}) was 37.1 ± 22.3 h*ng/mL and the mean ± SD average plasma concentration (C_{avg}) was 3.1 ± 1.9 ng/mL.

Distribution

Plasma protein binding of clascoterone is 84% to 89% and is independent of concentrations, in vitro.

Elimination

Metabolism

Following topical treatment with WINLEVI cream, the plasma concentrations of cortexolone, a possible primary metabolite of clascoterone, were detectable and generally below or near the lower limit of quantitation (0.5 ng/mL) in subjects ≥12 years of age with acne vulgaris.

The in vitro study indicated that incubation of 10 µmol/L clascoterone with human cryopreserved hepatocytes generated cortexolone as the possible primary metabolite and other unidentified metabolites, including conjugated metabolites.

Excretion

Excretion of clascoterone has not been fully characterized in humans.

Specific Populations

Pediatric Patients

In adolescent subjects ≥ 12 to <18 years of age (n=22) after 2 weeks of twice daily treatment with mean dose of approximately 6 grams of WINLEVI cream (or mean dose of approximately 4 grams in younger, smaller subjects), steady-state concentrations of clascoterone were achieved by Day 5. Clascoterone systemic exposure in adolescents was similar to those observed in adults.

Drug Interaction Studies

Clinical Studies

No clinical studies evaluating the drug interaction potential of WINLEVI cream have been conducted.

In Vitro Studies

CYP Enzymes: Clascoterone inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 with an IC_{50} value of >40 µM. Clascoterone up to 30 µM did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that WINLEVI cream has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Clascoterone cream (0.1%, 1%, or 5%) was not carcinogenic after daily topical administration in a 2-year carcinogenicity study in rats. An increased incidence of the non-neoplastic finding of atrophy of the skin and subcutis at the application site was reported in males and females treated with 1% and 5% clascoterone cream.

Clascoterone was not mutagenic in the Ames reverse mutation assay and was not clastogenic in the in vitro human lymphocyte chromosomal aberration assay. In rats, clascoterone administered via subcutaneous injection did not induce micronuclei in the bone marrow at 500 or 1000 mg/kg but a slight increase in micronuclei occurred in 2 of 5 rats at 2000 mg/kg. The response was considered equivocal. Overall, the weight of evidence indicates that clascoterone does not represent a genotoxic risk.

In a fertility and early embryonic development study in rats, clascoterone was administered subcutaneously at doses of 0.5, 2.5, or 12.5 mg/kg/day from 2 – 4 weeks before mating through mating. Clascoterone increased pre-implantation loss at 12.5 mg/kg/day (163 times the MRHD

based on AUC comparison). Clascoterone had no effects on mating or fertility in rats at doses up to 12.5 mg/kg/day (163 times the MRHD based on AUC comparison). No effects were noted on development at doses up to 2.5 mg/kg/day (33 times the MRHD based on AUC comparison).

12 CLINICAL STUDIES

The safety and efficacy of WINLEVI cream 1% applied twice daily for 12 weeks for the treatment of acne vulgaris were assessed in two identically-designed, multicenter, randomized, double-blind, vehicle-controlled clinical trials (Trial 1 [NCT02608450] and Trial 2 [NCT02608476]) enrolling 1440 subjects with facial acne vulgaris. The trials enrolled subjects 9 years or older with Investigator's Global Assessment (IGA) of moderate or severe facial acne vulgaris (score of 3 or 4), 30 to 75 inflammatory lesions (papules, pustules and nodules), and 30 to 100 non-inflammatory lesions (open and closed comedones).

A total of 1421 subjects 12 years and older with facial acne vulgaris were enrolled. Of these subjects, 641 (45%) were 12 to 17 years of age, and 780 (55%) were 18 years of age or older. In addition, 62% of the subjects were female, and 91% were Caucasian. At baseline, subjects had a mean inflammatory lesion count of 42.4 and a mean non-inflammatory lesion count of 61.4. Additionally, approximately 83% of subjects had an IGA score of 3 ("moderate").

Efficacy was assessed at Week 12 by the proportion of subjects in each treatment group with at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 (clear) or 1 (almost clear), absolute change and percent change from baseline in non-inflammatory and inflammatory lesions. The IGA success rate and mean absolute and percent reduction from baseline in acne lesion counts after 12 weeks of treatment for subjects 12 years of age and older are presented in the following table.

Table 2. Clinical Efficacy of WINLEVI Cream 1% in Subjects with Acne Vulgaris at Week 12

	Trial 1		**Trial 2**	
	WINLEVI Cream 1% N=342	**Vehicle Cream N=350**	**WINLEVI Cream 1% N=367**	**Vehicle Cream N=362**
IGA Success[a]	18.8%	8.7%	20.9%	6.6%
Difference from Vehicle	10.1%		14.3%	
(95% CI)	(4.1%, 16.0%)		(8.9%, 19.7%)	
Non-inflammatory Lesions				
Mean Absolute Reduction	20.4	13.0	19.5	10.8
Difference from Vehicle	7.3		8.7	
(95% CI)	(3.5, 11.1)		(4.5, 12.4)	
Mean Percent Reduction	32.6%	21.8%	29.6%	15.7%
Difference from Vehicle	10.8%		13.8%	
(95% CI)	(3.9%, 17.6%)		(7.5%, 20.1%)	
Inflammatory Lesions				
Mean Absolute Reduction	19.3	15.4	20.1	12.6
Difference from Vehicle	3.9		7.5	
(95% CI)	(1.3, 6.5)		(5.2, 9.9)	
Mean Percent Reduction	44.6%	36.3%	47.1%	29.7%
Difference from Vehicle	8.3%		17.5%	
(95% CI)	(2.2%, 14.4%)		(11.8%, 23.1%)	

[a] Investigator Global Assessment (IGA) success was defined as at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 (clear) or 1 (almost clear).

13 LIST OF EXCIPIENTS

Cetyl alcohol, Mono- and di- glycerides, Mineral oil, Propylene glycol, Vitamin E, Edetate disodium, Polysorbate 80, Citric acid Monohydrate and Purified water

14 HOW SUPPLIED/STORAGE AND HANDLING
WINLEVI cream 1% is supplied in an epoxy-lined aluminum blind-end tube with a polypropylene cap closure:
60-gram tube
30-gram tube
10-gram tube
2-gram tube

Store the product in a refrigerator at 2ºC to 8ºC. Do not freeze. After opening, store at or below 30ºC, away from direct sunlight and heat. Discard unused portion after one month from first opening.

15 SHELF-LIFE
36 months

16 Manufactured by:
Cosmo S.P.A.
Via C. Colombo, 1,
Lainate, Milan,
20045, Italy
For:
Cassiopea SpA
Via Cristoforo Colombo 1,
Lainate-Milano,
Italy 20045

17 Name and Address of Product Registration Holder:
Singapore
Hyphens Pharma Pte Ltd
16 Tai Seng Street, Level 4,
Singapore 534138

Malaysia
Hyphens Pharma Sdn Bhd
C-L2-01, Block C, Axis Business Park,
No. 10, Jalan Bersatu 13/4,
46200 Petaling Jaya, Selangor
Malaysia

Philippines
Hyphens Pharma Philippines, Inc.
16th Floor, Unit 1606, Orient Square Bldg.,
F. Ortigas Jr. Road, Ortigas Center, Pasig City
Philippines

18 Date of the Revision of the Text:
08/2024