PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr WINLEVI®

Clascoterone cream

1% w/w, Topical

Anti-Androgens

Sun Pharmaceutical Industries Limited
Sun House, Plot 201 B/1
Western Express Highway, Goregaon (E)
Mumbai - 400 063
Maharashtra, India

Date of Initial Authorization:

Jun 15, 2023

Imported and Distributed by:
Sun Pharma Canada Inc.
Brampton, ON L6T 1C1

Submission Control Number: 265619

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

WINLEVI (clascoterone) is indicated for:

- the topical treatment of *acne vulgaris* in patients 12 years of age and older.

1.1 Pediatrics

Pediatrics (12 to <18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of WINLEVI in pediatric patients aged 12 to <18 years have been established. Therefore, Health Canada has authorized an indication for pediatric use in this age group (see 7.1.3 Pediatrics).

Pediatrics (<12 years): The safety and efficacy of WINLEVI have not been established in pediatric patients under 12 years of age (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65years): The clinical studies did not include participants ≥ 65 years of age. Thus, the clinical studies did not determine whether patients ≥ 65 years of age respond differently from younger patients.

2 CONTRAINDICATIONS

WINLEVI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose per application is up to approximately 1 gram, which corresponds to 2 fingertip units. The recommended dosing regimen for WINLEVI is to apply a thin uniform layer of cream twice per day, in the morning and the evening, over the area prone to acne, as instructed by a health professional. Do not spot treat for optimal efficacy.

4.4 Administration

Cleanse the entire area to be treated and dry gently. After the skin is dry, apply a thin uniform layer of WINLEVI twice per day, in the morning and in the evening, over the area prone to acne, as instructed by a health professional.

The recommended dose per application is up to approximately 1 gram, which corresponds to 2 fingertip units. Each fingertip unit (approximately 0.5 g) is the amount of cream squeezed along the index finger from the tip to the first joint. When spread on the skin, the cream is expected to cover an area

approximately the size of two adult palms or one adult face.

Hands should be washed before and after applying WINLEVI cream.

Avoid accidental transfer of WINLEVI into eyes, lips, mouth, corners of the nose, or other mucous membranes. If contact with mucous membranes occurs, rinse immediately and thoroughly with water.

4.5 Missed Dose

If patients forget to take a dose of WINLEVI, they should be instructed to apply the next dose at the usual time. Patients should be instructed to not apply a double dose to make up for forgotten doses.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Topical	Cream / 1% w/w	Cetyl alcohol, citric acid monohydrate, edetate disodium, DL- alpha tocopherol (vitamin E), mineral oil, mono- and di- glycerides, polysorbate 80, propylene glycol, and water

Description

Each gram of WINLEVI contains 10 mg of clascoterone in a white to almost white cream.

WINLEVI is supplied in 30 gram and 60 gram aluminum tubes. Health professional samples are supplied in 2 gram and 10 gram aluminum tubes.

7 WARNINGS AND PRECAUTIONS

General

WINLEVI is for external use only. Not for ophthalmic, oral or vaginal use.

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

Avoid accidental transfer of WINLEVI into eyes, lips, mouth, corners of the nose, or other mucous membranes. If contact with mucous membranes occurs, rinse immediately and thoroughly with water.

Endocrine and Metabolism

Hypothalamic-pituitary-adrenal (HPA) axis suppression was observed and may occur during or after treatment with clascoterone. All Phase 2 maximum use clinical-trial subjects with HPA-axis suppression returned to normal HPA axis function 4 weeks after stopping treatment (see 7.1.3 Pediatrics; 10.2

Pharmacodynamics). Conditions which augment systemic effects include use over large surface areas, prolonged use, concomitant use of corticosteroid-containing products, and the use of occlusive dressings. Pediatric patients may be more susceptible.

If HPA axis suppression is suspected, consider withdrawing the drug.

Reproductive Health: Female and Male Potential

See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

Skin

WINLEVI may induce local irritation (edema, erythema/redness, pruritus, scaling/dryness, skin atrophy, stinging/burning, striae rubrea, telangiectasia). 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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on the use of WINLEVI 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 MRHD, respectively, increased malformations in rats and post-implantation loss and resorptions in rabbits (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

No studies were conducted to determine the presence of clascoterone or its metabolite in human or animal milk, the effects on the breastfed infant or the effects on milk production. It is unknown if the drug is excreted in human milk. Precaution should be exercised because many drugs are excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical benefit from clascoterone and any potential adverse effects on the breastfed child from clascoterone.

7.1.3 Pediatrics

Pediatric patients may be more susceptible to systemic toxicity than adults when treated with WINLEVI.

Pediatrics (12 to <18 years): The safety and efficacy of WINLEVI for the topical treatment of *acne vulgaris* have been established in pediatric patients, aged 12 to <18 years (see 14.1 Clinical Trials by Indication).

The safety and efficacy of WINLEVI have not been established in pediatric patients under 12 years of age.

In a Phase 2 maximum use clinical study with WINLEVI administered at 4 to 6 times above the recommended daily dose for up to 2 weeks (and twice the maximal dose in the controlled trials on the face), biochemical HPA axis suppression was observed in 2/22 (9%) adolescent patients aged 12 to <18 years. The subjects returned to normal HPA axis response at follow-up 4 weeks after stopping the treatment (see 10.2 Pharmacodynamics).

Pediatrics (<12 years):

WINLEVI is not authorized in pediatric patients under 12 years of age.

Pediatric patients under 12 years of age may be more susceptible to HPA axis suppression and hyperkalemia (see 10.2 Pharmacodynamics).

7.1.4 Geriatrics

Clinical studies of WINLEVI did not include patients aged 65 years of age and over to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In two identical multicenter, randomized, double-blind, vehicle-controlled trials, 1421 patients 12 years and older with facial *acne vulgaris* applied WINLEVI or vehicle (placebo cream) twice daily to the entire face for 12 weeks.

The most frequently reported treatment-emergent adverse events (referred to as local skin reactions (LSRs)) that occurred in ≥ 10% of WINLEVI-treated patients versus vehicle were erythema (12.2% vs 15.4%) and scaling/dryness (10.5% vs 10.4%). Most of the treatment-emergent LSRs were trace or mild in severity.

In maximum-use Phase 2 studies, less common adverse reactions were HPA-axis suppression and hyperkalemia (see 10.2 Pharmacodynamics).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates were observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

There were no adverse events reported as adverse drug reactions in > 1% of patients.

Local skin reactions (edema, erythema/redness, pruritus, scaling/dryness, skin atrophy, stinging/burning, striae rubrea, telangiectasia) were observed during the 12-week treatment and occurred in a similar percentage of patients treated with vehicle. Local skin reactions reported by ≥ 1% of patients treated with WINLEVI are shown in the following table.

Table 2 - Incidence of New or Worsening Treatment-Emergent Adverse Events (referenced as Local Skin Reactions)* Reported by ≥ 1% of Patients Treated with WINLEVI Cream After Day 1 in 12-Week Controlled Phase 3 Clinical Trials[a] – Aged 12 years and older

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

* Local Skin Reactions (LSRs) are defined in the clinical trials by the adverse events identified in the above table. Causality assessment was not completed for LSRs.

[a] Pooled Data of Trial 1 and Trial 2; The median age of patients who experienced new or worsening LSRs is 18 years of age (age range: 12 to 50 years of age).

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

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In the pooled Phase 3 studies, in patients aged 12 to <18 years of age, there were no adverse reactions reported in > 1% of patients. The TEAEs reported in ≥ 1% of patients aged 12 to <18 years in the pooled Phase 3 studies, and more often with WINLEVI, were headaches (1.3% WINLEVI, 0.3% vehicle).

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions associated with the use of WINLEVI were identified in clinical trials and the long-term safety study. The events are categorized by body system.

Reproductive system and breast disorders: polycystic ovaries

Skin and subcutaneous tissue disorders: hair colour changes

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

In clinical trials, the types of adverse reactions seen with WINLEVI were comparable in adult and pediatric patients.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Clinical laboratory evaluations were not performed in the Phase 3 studies.

In maximum-use Phase 2 studies, the following abnormal laboratory findings were observed:

Endocrine and Metabolism: hypothalamic-pituitary-adrenal (HPA) axis suppression, hyperkalemia (observed in subjects aged 9 to <12 years)

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Clascoterone inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 with an IC_{50} value of >40 µM. Clascoterone up to 50 µM did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that WINLEVI has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

9.4 Drug-Drug Interactions

Interactions with other drugs, including other topical medications, have not been established. Caution should be exercised in using WINLEVI along other drugs known to suppress the HPA axis (e.g., topical or inhaled corticosteroids).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Clascoterone is an androgen receptor inhibitor. Androgen receptor inhibitors may reduce sebaceous gland activity. 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), adolescent (n=22), and pediatric (n=27) patients with *acne vulgaris* following twice daily application of WINLEVI for 2 weeks in two maximum use pharmacokinetic studies. 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, 2/22 (9%) of adolescent and 2/23 (8.7%) of pediatric patients (< 12 years of age) at Day 14. All patients returned to normal HPA axis function at follow-up 4 weeks after the end of treatment. No subject experienced clinical signs and symptoms of adrenal suppression or associated complications.

Potassium

Overall, shifts from normal to elevated potassium levels were observed in 3.6% (17/468) of clascoterone-treated patients and 3.9% (4/103) of vehicle-treated patients (age range: 12 to 64). In a Phase 2 maximum use clinical study with WINLEVI administered above the recommended daily dose for up to 2 weeks, an increase in plasma potassium levels (hyperkalemia) was observed in 9/27 (33%) subjects aged 9 to <12.

Cardiac Electrophysiology

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

10.3 Pharmacokinetics

Absorption:

Following topical treatment of WINLEVI for 2 weeks with a mean dose of approximately 6 grams applied twice daily to adult patients 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*.

Metabolism:

Following topical treatment with WINLEVI, 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 patients ≥9 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.

Elimination:

Excretion of clascoterone has not been fully characterized in humans.

Special Populations and Conditions

- **Pediatrics**

In adolescent patients 12 to <18 years of age (n=22) after 2 weeks of twice daily treatment with mean dose of approximately 6 grams of WINLEVI per application (or mean dose of approximately 4 grams per application 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 (see Absorption).

- **Geriatrics**: No studies were conducted in patients ≥65 years of age (see 7.1.4 – Geriatrics).

11 STORAGE, STABILITY AND DISPOSAL

Prior to Dispensing: Store the product in a refrigerator between 2°C and 8°C. Do not freeze.

Dispensing Instructions for the Pharmacist: Direct the patient to store the product while in use at room temperature (20°C to 25°C). Do not freeze. Discard the unused product 180 days after the date of dispensing or 6 months after first opening, whichever is sooner.

Keep out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for WINLEVI.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

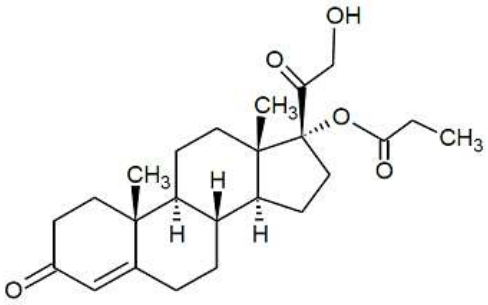
Drug Substance

Proper/Common name: Clascoterone

Chemical name: Cortexolone-17α propionate

Molecular formula and molecular mass: $C_{24}H_{34}O_5$; 402.5 g/mol

Structural formula:



Physicochemical properties: Clascoterone is a white to almost white powder, practically insoluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Acne vulgaris

Table 3 - Summary of Patient Demographics for Phase 3 Clinical Trials in *acne vulgaris*

Study #	Study design	Dosage, route of administration and duration	Study patients (n)	Mean age (Range)	Sex n (%)
CB-03-01/25 (Trial 1)	Phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study	WINLEVI, 1% cream, Topical, twice daily, 12 weeks	Total: 353 Patients ≥12 years: 342	Total: 20.0 years (10 – 58) Patients ≥12 years: 20.3 years (12 – 58)	Total: Female: 221 (62.6) / Male: 132 (37.4) Patients ≥12 years: Female: 211 (61.7) / Male: 131 (38.3)
		Vehicle Topical, twice daily, 12 weeks	Total: 355 Patients ≥12 years: 350	Total: 19.9 years (9 – 50) Patients ≥12 years: 20.0 years (12 – 50)	Total: Female: 215 (60.6) / Male: 140 (39.4) Patients ≥12 years: Female: 210 (60.0) / Male: 140 (40.0)
CB-03-01/26 (Trial 2)	Phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study	WINLEVI, 1% cream, Topical, twice daily, 12 weeks	Total: 369 Patients ≥12 years: 367	Total: 19.3 years (10 – 50) Patients ≥12 years: 19.4 years (12 – 50)	Total: Female: 243 (65.9) / Male: 126 (34.1) Patients ≥12 years: Female: 242 (65.9) / Male: 125 (34.1)
		Vehicle Topical, twice daily, 12 weeks	Total: 363 Patients ≥12 years: 362	Total: 19.0 years (11 – 42) Patients ≥12 years: 19.0 years (12 – 42)	Total: Female: 221 (60.9) / Male: 142 (39.1) Patients ≥12 years: Female: 220 (60.8) / Male: 142 (39.2)

The safety and efficacy of WINLEVI applied twice daily for 12 weeks for the treatment of *acne vulgaris* were assessed in two identically designed, multicenter, randomized, double-blind, vehicle-controlled, parallel-group Phase 3 clinical trials (Trial 1 and Trial 2) enrolling 1440 patients with facial *acne vulgaris*. The trials enrolled patients 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). Patients with 2 facial nodules or nodulocystic acne were excluded. Concurrent acne treatment was not allowed.

A total of 1421 patients 12 years and older with facial *acne vulgaris* were enrolled. The treatment groups in each study were well-balanced with similar demographic and baseline characteristics in the intent-to-treat (ITT) population, both within and between Trial 1 and Trial 2. Of these subjects, 641 (45.1%) were 12 to <18 years of age, and 780 (54.9%) were 18 years of age or older. In addition, 62.1% of the patients were female, and 90.6% were Caucasian. At baseline, patients had a mean inflammatory lesion count of 42.4 and a mean non-inflammatory lesion count of 61.4. Approximately 83.3% of patients had an IGA score of 3 ("moderate"), and 16.7% had an IGA score of 4 ("severe").

Efficacy was assessed at Week 12 by the co-primary efficacy endpoints which included the proportion of patients in each treatment group with at least a 2-point reduction in IGA compared to baseline and a final IGA score of 0 (clear) or 1 (almost clear); absolute change from baseline in non-inflammatory lesion count (NILC) and inflammatory lesion count (ILC). Secondary efficacy endpoints included absolute and percent change from baseline in total lesion count (TLC); percent change from baseline in non-inflammatory and inflammatory lesion count.

The IGA success rate and mean absolute reduction from baseline in acne lesion counts after 12 weeks of treatment for patients 12 years of age and older are presented in the Table 4 below.

Table 4 - Clinical Efficacy of WINLEVI Cream 1% in patients (aged 12 and older) with Acne Vulgaris at Week 12

Co-Primary Endpoints	Trial 1		Trial 2	
	WINLEVI N=342	**Vehicle N=350**	**WINLEVI N=367**	**Vehicle N=362**
Proportion of patients with IGA Success[a]				
n (%)	55 (16.1)	24 (6.8)	69 (18.8)	17 (4.7)
Adjusted proportions[b]	18.8%	8.7%	20.9%	6.6%
Adjusted odds ratio Point estimate (95% Confidence limits), p-value[b]	2.42 (1.46, 4.01), p = 0.0007		3.77 (2.20, 6.45), p = 0.0001	
Absolute change from baseline in Non-inflammatory Lesion Count				
LS means[c]	-20.4	-13.0	-19.5	-10.8
Difference between treatments (95% Confidence limits), p-value[c]	-7.3 (-11.1, -3.5), p = 0.0002		-8.7 (-12.6, -4.7), p < 0.0001	
Absolute change from baseline in Inflammatory Lesion Count				
LS means[c]	-19.3	-15.4	-20.1	-12.6
Difference between treatments (95% Confidence limits), p-value[c]	-3.9 (-6.5, -1.3), p = 0.0034		-7.5 (-9.9, -5.2), p < 0.0001	

The results for the secondary endpoints were similar between the 2 studies. The results were statistically significant compared to vehicle in both studies (Table 5).

Table 5 - Results of Secondary Endpoints for Trial 1 and Trial 2 in Patients with *acne vulgaris* Aged 12 and older at Week 12 (ITT)

Secondary Endpoints	Trial 1		Trial 2	
	WINLEVI N=342	Vehicle N=350	WINLEVI N=367	Vehicle N=362
Absolute change from baseline in Total Lesion Count				
LS means[a]	-40.0	-28.6	-40.5	-23.6
Difference between treatments (95% Confidence limits), p-value[a]	-11.4 (-16.8, -6.0), p < 0.0001		-16.9 (-22.4, -11.4), p < 0.0001	
Percent change from baseline Total Lesion Count				
LS means[a]	-38.1	-28.3	-38.0	-22.1
Difference between treatments (95% Confidence limits), p-value[a]	-9.8 (-15.2, -4.4), p = 0.0004		-15.9 (-21.2, -10.6), p < 0.0001	
Percent change from baseline in Non-inflammatory Lesion Count				
LS means[a]	-32.6	-21.8	-29.6	-15.7
Difference between treatments (95% Confidence limits), p-value[a]	-10.8 (-17.6, -3.9), p = 0.0021		-13.8 (-20.2, -7.5), p < 0.0001	
Percent change from baseline in Inflammatory Lesion Count				
LS means[a]	-44.6	-36.3	-47.1	-29.7
Difference between treatments (95% Confidence limits), p-value[a]	-8.3 (-14.4, -2.2), p = 0.0080		-17.5 (-23.1, -11.8), p < 0.0001	

[a] LS = Least square; Least square mean and p-value are based on analysis of covariance with treatment and analysis center as fixed effects, and baseline value as a covariate

Given the limitations of subgroup analyses, the results of such analyses should be interpreted with caution. When stratified by Fitzpatrick skin type (I, II, III versus IV, V, VI), ethnicity, and race, there is a trend of less favourable effect estimates in racialized subgroups. This could be due to between-group differences in acne assessments, treatment effects, and/or chance.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In acute intravenous (IV) and subcutaneous (SC) toxicity studies in mice, a single IV administration produced a median lethal dose (LD_{50}) of > 100 mg/kg and a single SC administration produced an LD_{50} of > 1000 mg/kg. In female Wistar rats, animals dosed 30 mg/kg (IV) showed slight or moderate sedation and deep respiration immediately after dosing which was transient and no longer present after 0.5 hour. Three out of seven rats dosed with 100 mg/kg (IV) died shortly after dosing. Clinical signs noted were ruffled fur, poor coordination, ventral recumbency, tachypnea and convulsions within first 30 minutes post dose and resolved by Day 2. LD_{50} was determined to be > 100 mg/kg.
In female Wistar rats dosed 1000 mg/kg (SC), one animal exhibited scabs and/or wounds and one animal developed erythema at the injection site. LD_{50} was determined to be > 1000 mg/kg. Transient weight loss was observed in all these studies, however, animals recovered by Day 15.

In estrogen-pretreated immature female rabbits, clascoterone administered subcutaneously at 1 mg/kg showed progestational activity characterized by endometrial stimulation and increased uterine weight.

In a 28-day dermal toxicity study in rabbits, hematological and clinical chemistry changes consistent with glucocorticoid effects were seen in animals treated with 50 mg/kg/day, including decreased lymphocytes, increased plasma phospholipids, increased albumin, and increased enzyme levels (AST, ALT, ALP), along with increased liver weight and decreased adrenal weight. Leucopenia was also observed in rats treated with 25 mg/kg/day in a 13-week subcutaneous toxicity study.

In a 26-week repeat-dose toxicity study in Wistar rats, no test article-related changes that could be considered as adverse occurred following repeated SC injection of clascoterone at any of the dose levels investigated (0.1, 0.5 and 2.5 mg/kg/day). The high dose of 2.5 mg/kg/day (associated with Day 182 AUC values of 298.61 and 173.19 ng·hr/mL in males and females, respectively) was considered the no-observed-adverse-effect-level (NOAEL) in this study.

In a 9-month dermal toxicity study in Göttingen minipigs, mild transient erythema was observed in some animals from both sexes at all dose levels (1%, 2.5% or 5%) of clascoterone, with a few isolated instances of moderate to severe erythema. The mean adrenal gland weight was lower in animals treated with 2.5% and 5% clascoterone cream, which correlated with adrenal cortical atrophy (in the zona reticularis and zona fasciculata); this was not fully reversible in males after the recovery period. Minimal to mild atrophy of the skin of animals treated with all dose levels of clascoterone was observed. The testes of one male in the 5% treatment group had minimal interstitial cell hypertrophy. Hair follicles in the treated skin were also in the resting stage more often compared to vehicle. These findings were not considered to be adverse, therefore the NOAEL was determined to be clascoterone 5% cream, the highest concentration tested (associated with Day 272 mean $AUC_{0\text{-}24}$ values of 401 and 269 ng·hr/mL in males and females, respectively).

Carcinogenicity: Clascoterone cream (0.1%, 1%, or 5%) was not carcinogenic after daily topical administration in a 2-year carcinogenicity study in rats. A slight increase in benign sebaceous cell adenoma at the topical application site was observed in males treated with 5% clascoterone cream. 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.

Genotoxicity: Clascoterone was not clastogenic in the *in vitro* human lymphocyte chromosomal aberration assay. In the Ames reverse mutation assay, a negative response was seen in all strains tested except TA98, in which a slight increase in revertants was noted at 333 µg/plate in the pre-incubation experiment. This response was considered equivocal. 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.

Reproductive and Developmental Toxicology: 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 decreased testicular sperm counts and increased caudal epididymis sperm counts in males 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).

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 (0.5% of fetuses examined) 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 (0.9% of fetuses examined) 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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr WINLEVI®

Clascoterone Cream 1%

Read this carefully before you start taking **WINLEVI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **WINLEVI**.

What is WINLEVI used for?

- WINLEVI is used on the skin (topical) to treat *acne vulgaris* in people 12 years of age and older.

How does WINLEVI work?

WINLEVI belongs to a group of medicines called androgen receptor inhibitors. The exact way that WINLEVI works is not known. It is thought to treat acne by blocking androgens in your skin from making too much sebum (oils that keep your skin moist).

What are the ingredients in WINLEVI?

Medicinal ingredients: clascoterone

Non-medicinal ingredients: cetyl alcohol, citric acid monohydrate, edetate disodium, DL-alpha tocopherol (vitamin E), mono- and di-glycerides, mineral oil, polysorbate 80, propylene glycol, and water.

WINLEVI comes in the following dosage form:

Cream 1%

Do not use WINLEVI if:

- you are allergic to clascoterone or any of its ingredients (**see <u>What are the ingredients in WINLEVI?</u>**)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take WINLEVI. Talk about any health conditions or problems you may have, including if you:

- were previously or are currently taking corticosteroid drugs
- have skin problems, including eczema, cuts or sunburn
- are pregnant or plan to become pregnant. It is not known if WINLEVI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if WINLEVI passes into breast milk. Talk to your healthcare professional about the best way to feed your baby during treatment with WINLEVI.

Other warnings you should know about:

- Avoid using skin products that may dry or irritate your skin such as:
    - medicated or abrasive soaps and cleansers
    - soaps, cleansers, and cosmetics that have strong skin drying effects
    - products that contain high amounts of alcohol
    - astringents (used to dry or shrink skin tissue), spices, or lime

You may experience adrenal suppression as a rare side effect of taking WINLEVI. This is where the adrenal gland does not make enough of certain hormones. Some people have no symptoms unless they are exposed to stress. If you experience a medical emergency (such as an infection) or have surgery, tell your healthcare professional that you are taking WINLEVI. Adrenal suppression may cause further issues in these cases. See the "Serious side effects and what to do about them" table, below.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to use WINLEVI:

- Use WINLEVI exactly as your healthcare professional tells you to use it.
- Do not give WINLEVI to other people, even if they have the same symptoms you have. It may harm them.
- WINLEVI is to be used on the skin only (topical). Do not use WINLEVI in or on your eyes, mouth, or vagina.
- Do not apply WINLEVI on areas with cuts, scratches, rashes or sunburns.
- Avoid getting WINLEVI into your eyes, lips, mouth, corners of the nose, or mucous membranes. If contact with mucous membranes happens, rinse immediately and thoroughly with water.
- Before applying WINLEVI, gently wash and dry the entire area of the skin to be treated.
- Do not spot treat for best results.
- Wash your hands after applying WINLEVI.

Usual dose:

Apply a thin even layer of WINLEVI over the area prone to acne, twice a day, in the morning and in the evening. The recommended dose per application of WINLEVI is up to 1 gram (approximately the length of 2 fingertips). When spread on the skin, this should be enough to cover the size of two adult palms or one adult face.

Overdose:

If you think you, or a person you are caring for, have used too much WINLEVI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to apply a dose, the next dose should be applied at the usual time. Apply the same amount you usually would. Do not apply extra.

What are possible side effects from using WINLEVI?

- Local skin irritation such as itching, burning, skin redness, peeling, scaling, dryness or change of hair colour at the area of application.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Adrenal effects (may include one or several): Unexplained fatigue, weakness, nausea, stomach pain, or joint / muscle pain	**√**		
Adrenal effects (may include one or several): Unexplained weight loss, absence of menstruation, vomiting, impaired memory, depression, or altered mental state (psychosis). Talk to your healthcare professional if these symptoms appear, but you're not sure why.		**√**	

These are not all the possible side effects you may have when taking WINLEVI. If you experience any side effects not listed here, tell your healthcare professional.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Pharmacist: Store the product in a refrigerator between 2°C and 8°C. Do not freeze.

At home: Store at room temperature (20°C to 25°C). Do not freeze. Discard the unused product 180 days after the date of dispensing or 6 months after first opening, whichever is sooner.

Keep out of the reach and sight of children.

If you want more information about WINLEVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sunpharma.com/canada, or by calling 1-844-924-0656.

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