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)].*

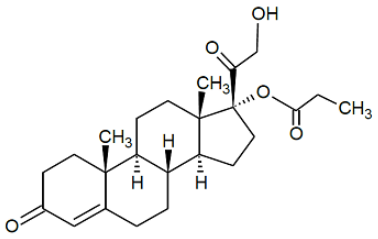
8.4 Geriatric Use

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:
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18 Date of the Revision of the Text:
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