

Brand Name: Winlevi

Generic Name: clascoterone cream 1%

Manufacturer: Cassiopea SpA¹

Drug Class: androgen receptor inhibitor

Uses:

Labeled: acne vulgaris^{2,3}

Unlabeled: n/a³

Mechanism of Action: androgen receptor inhibitor that decreases sebum production and inflammation.³

Pharmacokinetics:

Tmax	14 days ⁴
Vd	Not specified
T _{1/2}	Not specified
Clearance	Not specified
Protein Binding	84-89% ⁴
Bioavailability	Not specified

Metabolism: inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.⁴

Elimination: Upon topical application, clascoterone is quickly hydrolyzed in the epidermis.⁵

Efficacy:^{5,6}

Hebert A, Thiboutot D, Stein Gold L, Cartwright M, Gerloni M, Fragasso E, Mazzetti A. Efficacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients With Facial Acne: Two Phase 3 Randomized Clinical Trials. *JAMA Dermatol.* 2020 Jun 1;156(6):621-630.

Design: Randomized, double-blind, placebo-controlled, multi-center, phase 3 study

Description: Two identical trials, (NCT02608450 and NCT02608476), were used to determine the safety and efficacy of clascoterone cream. To be included in the study participants had to be male or non-pregnant female that are at least 9 years old, have an Investigator's Global Assessment (IGA) score of 3 or 4 [0 (clear) to 4 (severe)], have facial acne vulgaris, with at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules) and 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones), Subject has used the same type and brand of make-up, other facial products (exclusive of RX/OTC acne cleansers) and hair products for at least one month prior to the baseline visit, and agrees to continue his/her other general skin and hair care products and regimen for the entire study.

Between the two trials a total of 1440 patients were randomized to receive clascoterone 1% cream – 1g applied to the face twice daily for 12 weeks or placebo. Treatment success was defined as an Investigator's Global Assessment score of 0 (clear) or 1 (almost clear), and a 2-grade or greater improvement from baseline and absolute change from baseline in noninflammatory and inflammatory lesion counts at week 12. Considerably more patients receiving clascoterone cream 1%, vs vehicle achieved treatment success at week 12 (NCT02608450, 18.4% vs 9.0%; and NCT02608476, 20.3% vs 6.5%, respectively). The absolute change from baseline in non-inflammatory and inflammatory lesion count at week 12 were also substantially greater with use of clascoterone cream 1% vs vehicle. Safety measures included adverse event frequency and severity.

Limitations: Limitations of these phase 3 studies include the small sample sizes available for subgroup analyses, such as race and age, which limit the conclusions that can be drawn for subpopulations. Concomitant acne treatment was not allowed thus limiting the understanding of optimal combination therapies. Lastly, patient reported outcomes were not included as an outcome but should be considered in future studies.

Conclusion: Use of clascoterone cream, 1%, for acne treatment appears to demonstrate favorable efficacy and safety with low adverse event rates. Additional studies assessing long term use would be needed to determine its place in therapy.

Mazzetti A, Moro L, Gerloni M, Cartwright M. Pharmacokinetic Profile, Safety, and Tolerability of Clascoterone (Cortexolone 17-alpha propionate, CB-03-01) Topical Cream, 1% in Subjects With Acne Vulgaris: An Open-Label Phase 2a Study. J Drugs Dermatol. 2019 Jun 1;18(6):563. PMID: 31251549.

Design: open label, multi-center study

Description: 42 subjects at least 12 years old with moderate to severe acne (IGA grade 3-4) on the face, chest, and/or back. Cohort 1 (patients \geq 18 years old) and Cohort 2 (patients 12-18 years old), applied clascoterone topical cream 1% twice daily for 14 days. Primary safety endpoints were hypothalamic-pituitary-adrenal (HPA) axis response to cosyntropin via a Cosyntropin Stimulation Test (CST) at day 1 (screening) and at day 14 and PK evaluation including concentration-time profiles of clascoterone and cortexolone in plasma. Secondary safety endpoints included clinical laboratory testing, local and systemic adverse events, physical exam/vital signs, and electrocardiogram. Of the 42 subjects enrolled, 7% (three subjects; 1 adult and 2 children), demonstrated an abnormal HPA axis response with post-stimulation serum cortisol levels ranging from 14.9 to 17.7 $\mu\text{g/dL}$ at day 14. All returned to normal HPA axis function, four weeks after day 14. None showed clinical evidence of adrenal suppression. Clascoterone plasma concentrations achieved PK steady state by day 5. Clascoterone systemic exposure was similar between both cohorts. At steady-state, plasma concentrations increased \sim 1.8 to 2.1-fold versus first dose with mean (coefficient of variation [CV] %) maximum plasma concentrations of 4.4 ng/mL (67%) and 4.6 ng/mL (103%) in Cohort 1 and Cohort 2, respectively. Cortexolone plasma concentrations trended below the lower limit of

quantitation (0.5 ng/mL) in both cohorts. Local skin reactions were mostly mild, with only one moderate case of pruritus. There were nine AEs categorized as follows: definitely related (N=2), probably related (N=4), unlikely/not related (N=3), to clascoterone.

Limitations: The study population was very small which makes it hard to extrapolate results. The duration was short so we cannot assess safety profile for long term use. The study did not analyze efficacy results.

Conclusion: This study shows that clascoterone 1% is safe in adults and children over 12 years old that have moderate to severe acne vulgaris when used twice a day for 14 days.

Contraindications: specific contraindications have not been determined.⁴

Precautions:

Administration: Do not apply to cuts, abrasions, eczematous or sunburned skin.⁴

Dermatologic: local irritation may occur; limit concomitant use with other potentially irritating topical products.⁴

Endocrine and metabolic: Hypothalamic-pituitary-adrenal (HPA) axis suppression has been reported and may occur during or after therapy, especially when used over large surface areas, with prolonged use, and when used with occlusive dressings; increased risk of occurrence with pediatric patients. Therapy interruption may be necessary.⁴

Adverse Effects:

Common: Dry skin (10.5%), erythema (12.2%), and pruritis (7.7%)⁴

Serious: hypothalamic-pituitary-axis dysfunction, PCOS, hyperkalemia^{3,4}

Drug Interactions: no drug-drug interactions have been identified.^{3,4}

Dosing/Administration:

Adult: apply a thin layer topically to affected areas of the skin twice daily.^{3,4}

Pediatric: for children and adolescents 12 and older; apply a thin layer topically to affected areas of the skin twice daily; once in the morning and once in the evening.^{3,4}

Renal impairment: no dosage adjustments necessary^{3,4}

Hepatic impairment: no dosage adjustments necessary^{3,4}

Use in special populations:

Pregnancy: there is no FDA rating for safety in the pregnant population.⁴

Breastfeeding: Infant risk cannot be ruled out: Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when clascoterone is used during breast-feeding.^{3,4}

Pediatrics: children may absorb larger amounts after topical application and may be more prone to systemic effects. Prolonged use may affect growth velocity.³

Conclusion: Winlevi (clascoterone) is a topical cream approved by the FDA for the treatment of acne vulgaris in adults and children over 12 years old. Two randomized controlled trials showed

that patients with moderate to severe acne, using clascoterone had significantly higher treatment success than those patients not using clascoterone. It is important for further testing and studies to address drug interactions, safety in pregnancy, as well as any contraindications that may exist. It would also be important to compare clascoterone to current treatments for acne vulgaris. The cost of the medication is \$190 for a 100mg unit and \$550 for a 500mg unit. Clascoterone could be an effective option for treating acne vulgaris especially if other currently available treatment options have failed.

References:

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Prepared by: Kayla Ledsoe, Doctor of Pharmacy Candidate