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Drug Class Update with New Drug Evaluation: Acne Drugs

Date of Review: February 2021

Generic Name: Clascoterone Cream

Date of Last Review: June 2020
Dates of Literature Search: 12/26/2019 - 12/01/2020
Brand Name (Manufacturer): Winlevi (Cassiopea, Inc.)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The acne class has had one new approval, clascoterone cream, since it was last reviewed in 2019. The purpose of this update is to evaluate new comparative evidence for clascoterone cream for the treatment of acne vulgaris and any new data on comparative efficacy or harms in the acne class since the previous update. Acne conglobata, acne fulminans, and severe cystic acne are covered conditions under the Oregon Health Plan (OHP).

Research Questions:
1. What is the comparative efficacy and effectiveness of treatments for severe acne (**Appendix 1**; hormonal agents of oral contraceptives and spironolactone; clascoterone)?
2. What are the comparative harms of treatments for severe acne?
3. Are there subpopulations of patients in which a particular treatment for severe acne would be more effective or associated with less harm?

Conclusions:
- Recent Cochrane reviews evaluating azelaic acid and topical benzoyl peroxide support current policy.[1,2]
- Clascoterone was evaluated versus a placebo vehicle in moderate to severe acne in two fair quality trials.[3] Quality is limited by risk of bias (RoB) related to industry funding. Applicability is limited by lack of long-term data, lack of racial diversity in study population, and limitations related to placebo control rather than active control.
    - Clascoterone was superior versus vehicle for treatment success (Investigator's Global Assessment [IGA] scale minimum 2-point improvement from baseline AND a score of 0 [clear] or 1 [almost clear]; this is considered a clinically meaningful endpoint) at twelve weeks based on moderate quality evidence (study 1; 16.1% clascoterone patients vs. 7.0% vehicle patients, RR 2.3, 95% confidence interval [CI] 1.4 to 3.8, p<0.001, number needed to treat [NNT] 11; study 2; 18.7% clascoterone patients vs 4.7% vehicle patients, RR 3.7, 95% CI 2.2 to 6.3, p<0.001, NNT 8).
    - Clascoterone was superior versus vehicle for absolute change in non-inflammatory lesion count (NILC) at 12 weeks (study 1; Lesion count difference -6.4, 95% CI -10.3 to -2.6, p<0.001; study 2; lesion count difference -8.6, 95% CI -12.3 to -4.9, p<0.001). (moderate quality evidence)

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    - Clascoterone was superior versus vehicle for absolute change in inflammatory lesion count (ILC) at 12 weeks (study 1; lesion count difference -3.8, 95% CI -6.4 to -1.3, p=0.003; study 2; lesion count difference -7.4, 95% CI -9.8 to -5.1, p<0.001). (moderate quality evidence)
- Clascoterone has similar rates of local skin reactions (LSR) and treatment emergent adverse events (TEAE) compared to vehicle. Safety in pregnancy and risk of Hypothalamic-Pituitary-Adrenal (HPA) axis suppression with long-term use are unknown.

Recommendations:
- Clascoterone designated as non-preferred on Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan (PMDP).
- After review of costs in executive session, benzoyl peroxide (BPO) lotion and erythromycin/BPO gel (Benzamycin and generic) were made preferred, and BPO towelette was made non-preferred on PDL.

Summary of Prior Reviews and Current Policy
- Two high quality systematic reviews evaluated comparative efficacy and safety of oral isotretinoin with other acne vulgaris treatments. These reviews contain low- and very low-quality evidence due to various biases and methodological study limitations.
- Trifarotene has moderate quality evidence due to study limitations to support its use in moderate acne vulgaris. Quality is limited by unclear selection bias, high attrition bias, and bias related to industry funding. Applicability is limited by lack of racial diversity in study population and limitations related to placebo control rather than active control. Number needed to treat of 6 to 10 for treatment success as defined by trial protocol.
- With the exception of oral isotretinoin, there is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.
- Multiple therapies including topical and systemic products are used for the treatment of severe acne. Currently, trifarotene cream and other new single-source brand formulations are non-preferred on the preferred drug list (PDL) given lack of high-quality data to support use in severe acne.
- Prior authorization (PA) criteria for the Acne preferred drug list (PDL) class includes federal legend topical medications that have FDA approval and an OHA-funded indication for severe acne vulgaris and oral isotretinoin. Use is limited to funded conditions in the OHP **(Appendix 6)**.

Background:

Acne vulgaris (AV) is a chronic skin condition that affects approximately 50 million people in the United States.[4] It most commonly affects adolescents and young adults, but can continue into adulthood. Morbidity associated with acne can include permanent scarring, poor self-image, depression, and anxiety.[4] Acne vulgaris is characterized by noninflammatory open or closed comedones and inflammatory lesions.[5] These are generally located on the face, neck, back, chest, and upper arms.[5,6] Follicular hyperkeratinization, microbial colonization with *Cutibacterium acnes* (formerly *Propionibacterium acnes*), sebum production, and inflammatory factors involving innate and acquired immunity are all involved in the pathology of this condition.[4,5]

Acne conglobata and acne fulminans are two forms of severe acne. Acne conglobata is a severe form of nodular acne that involves recurrent abscesses and communicating sinuses and often results in disfiguring scars.[6] Acne fulminans is a severe variant of inflammatory acne that presents with severe ulceration and occasionally the systemic symptoms of fever and arthralgia.[6] Assessment is done by physical exam and includes a pattern-diagnosis system that evaluates not only the presence and frequency of certain lesions, but also complications such as drainage, hemorrhage, pain and other factors like occupational disability, psychosocial impact, and failure of response to previous therapies.[6]

Treatment for acne may include a variety of agents such as topical medications (i.e., retinoids, benzoyl peroxide, topical antibiotics, salicylic acid, azelaic acid, sulfacetamide), systemic or topical antibiotics (i.e., doxycycline, minocycline, erythromycin, azithromycin, clindamycin, trimethoprim, dapsone), hormonal agents (i.e. oral contraceptives, spironolactone, antiandrogens), and oral isotretinoin.[4,5,7] Choice of treatment depends on severity of disease. Isotretinoin, which has an associated iPLEDGE REMS program, is specifically FDA-approved for severe recalcitrant nodular acne and recommended for severe acne.[5,7] Other treatments for severe acne usually include combination therapy with multiple classes of medications which can also be used for mild or moderate acne.[5,7] These classes of medications are well-established and all have been FDA-approved for many years.

In clinical trials, patients are often described at baseline by Fitzpatrick skin phototypes. This system separates patients into 6 categories (I to VI) based on 2 components: skin tone when unexposed to sunlight and skin reaction to sunlight (e.g., burning and tanning).[7] Increasing Fitzpatrick numbers indicate a darker unexposed skin tone and increasing ability to tan with decreasing risk of burning during sun exposure.[7]

Clinically meaningful outcomes for acne assessment include quality of life (QoL) and symptom reduction as demonstrated by decreased lesion counts or lessened acne severity. While there is no universal grading system, and as many as 18 different grading scales are used in the literature, classification of acne is commonly described as mild, moderate, or severe.[4,6,8] These are delineated by frequency of papules or pustules and presence and frequency of nodules, as well as presence of hyperpigmentation and erythema.[6] The Physician's Global Assessment (PGA) is a 5-point scale (0-4) that was previously recommended by the Food and Drug Administration (FDA) to evaluate success in clinical trials of acne vulgaris treatment.[9] The scale defines the skin as clear, almost clear, mild, moderate, and severe with corresponding descriptions for each score based on number of comedones, papules, pustules, nodules, cysts and overall amount of face involved.[9] More recently, the FDA has given industry guidance to use the Investigator's Global Assessment (IGA) as an ordinal scale to assess overall severity.[10] The IGA is a 5- or 6-point scale (0-5) that grades hyperpigmentation and erythema as clear, almost clear, mild, moderate, severe, and very severe.[10] It should be used in conjunction with separate counting of inflammatory and noninflammatory lesions.[10] Though there seems to be no universally determined minimal clinically important difference for these outcomes, a consensus view of the authors of the European Evidence-Based Guidelines for Treatment of Acne suggested a minimal clinically important difference of 10% or greater reduction in lesion count as an efficacy outcome.[11] A final IGA assessment of 0 to 1 (clear to almost clear) and at least a 2-grade improvement from baseline is defined by the FDA as a clinically meaningful outcome.[10]

There are no QoL assessment tools recommended in the FDA guidance to industry[10], nor was it included in the current new drug evaluation. Development and validation of a patient reported outcome measure for assessing acne treatment in the clinic is an identified research gap.[4]

Table 1: Acne class patient claims from second quarter 2020

PDL status of initial medication claim	Patients with claims	Patients with paid claims for the requested medication or another within class within 90 days	Patients with denied claims
Preferred	361	55 (15%)	306 (85%)
Non-preferred	16	0	16 (100%)

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[12-15]

Cochrane-Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc, and fruit acid (alpha-hydroxy acid) for acne

The effects of various topical treatments for acne when compared to other topical treatments, placebo, or no treatment were assessed through May 2019.[1] Forty-nine randomized controlled trials (RCT) (n=3880) of ages 10-45 years with primarily female participants were included.[1] Of trials where severity was reported (n=2939), 75.7% had mild to moderate acne, the remaining had a mix severities with at least 334 patients having moderate, severe, or severe cystic acne.[1] Treatment duration was over 8 weeks for 59% of the included RCTs.[1] There were 26 RCT with high RoB in at least one domain, while most domains were low or unclear RoB.[1] Azelaic acid is the only agent on the OHP PMDP that will be reviewed here.

The primary outcome was participant's global self-assessment of acne improvement.[1] Azelaic acid is probably less effective than BPO (risk ratio [RR] 0.82, 95% CI 0.72 to 0.95; 1 study, n=351, moderate-quality evidence).[1] There is likely no or minimal difference between azelaic acid and tretinoin (RR 0.94, 95% CI 0.78 to 1.14; 1 study, n=289, moderate-quality evidence) and azelaic acid and clindamycin (RR 1.13, 95% CI 0.92 to 1.38; 1 study, n=229, low-quality evidence).[1] There is uncertainty regarding any difference between azelaic acid and adapalene (1 study, n=55, very low-quality evidence).[1]

Safety differences defined as total minor adverse events are unclear between azelaic acid and adapalene (1 study, n=55, very low-quality evidence) and benzoyl peroxide (1 study, n=30, very low-quality evidence).[1] There is no difference when compared to clindamycin (RR 1.5, 95% 0.67 to 3.35, 1 study, n=11, low-quality evidence).[1]

Cochrane-Topical benzoyl peroxide for acne

The effects of topical BPO monotherapy or in combination for acne on the face or trunk was assessed through February 2019.[2] One-hundred and twenty trials (n=29,592) were included.[2] Participants had a mean age of 18 to 30 years, 72 trials included participants with mild to moderate acne and 26 included participants with severe acne.[2] The treatment duration was up to 12 weeks in 108 trials, and high or unclear RoB was common for performance, detection, or attrition bias.[2]

The participant's global self-assessment of acne improvement and withdrawal due to adverse events were the primary outcome measures. BPO may be more effective than placebo or no treatment during 10 to 12 weeks of treatment (RR 1.27, 95% CI 1.12 to 1.45, 3 studies, n=2234, low-certainty evidence).[2] There is minimal to no difference between BPO and adapalene during 11 to 12 weeks of treatment (RR 0.99, 95% CI 0.90 to 1.10, 5 studies, n=1472, low-certainty evidence) and clindamycin during 10 weeks of treatment (RR 0.95, 95% 0.68 to 1.34, 1 study, n=240, low-certainty evidence).[2] Treatment discontinuation over 10 to 12 week treatment durations may be higher with BPO than placebo or no treatment (RR 2.13, 95% CI 1.55 to 2.93, 24 studies, n=13,744, low-certainty evidence).[2] Reasons for discontinuation were erythema, pruritus, and skin burning.[2] Only very low-certainty evidence is available for withdrawal due to adverse events of BPO when compared to adapalene, clindamycin, erythromycin, and salicylic acid.[2] None of these comparisons were statistically significant.[2]

New Guidelines:
No new guidelines were identified for review.

New Formulations or Indications:
None

New FDA Safety Alerts:
None

Randomized Controlled Trials:
A total of 27 citations were manually reviewed from the initial literature search.[16-42] After further review, 27 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

<u>NEW DRUG EVALUATION:</u>

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Clascoterone is the first androgen receptor antagonist approved for the topical treatment of acne vulgaris in patients 12 years and older.[43]

Clascoterone has been evaluated in two phase 3, randomized, multicenter, parallel group, double-blind, vehicle-controlled trials of identical design to assess use for the treatment of moderate to severe facial acne vulgaris [Study 1 (NCT 02608450), Study 2 (NCT02608476)].[3,44-46] Patients 9 years of age and older were treated for up to 12 weeks with twice daily clascoterone 1% cream or a placebo vehicle cream. Patients were required to have been on a consistent skincare program for one month prior to, and for the duration of the study. Efficacy was assessed by a 5-point IGA for face in patients with a baseline score of 3 (moderate) or 4 (severe). The IGA is a static evaluation recommended by the FDA for acne severity. FDA guidance recommends limiting efficacy assessment to the face, as it is the most frequent site of involvement.[10] The primary endpoint of treatment success required IGA scale minimum 2-point improvement from baseline AND a score of 0 (clear) or 1 (almost clear). Reduction of ILC and NILC are additional primary endpoints. Secondary endpoints were a reduction of total lesion count (TLC) and percentage change of ILC, NILC, and TLC.[3]

All primary and secondary endpoints are statistically significant in favor of clascoterone for both studies. Success at twelve weeks occurred in 16.1-18.7% clascoterone patients and 4.7-7.0% of vehicle patients (study 1; RR 2.3, 95% CI 1.4 to 3.8, p<0.001; study 2; RR 3.7, 95% CI 2.2 to 6.3, p<0.001). Absolute change in lesion count was greater for clascoterone than vehicle for NILC by an average of -6.4 and -8.6 lesions, ILC by -3.8 and -7.4 lesions, and TLC by -10.3 and -16.4 lesions.[3] See **Table 4** for full results.

Limitations for both of these studies include short duration of therapy of 12 weeks, limited applicability outside of a white patient population, and a significant attrition rate without known cause. Additionally, while statistically significant compared to placebo, the overall success rates were quite low at 16.1% and 18.7%. Given the number of other acne therapies already available, comparison against an active comparator would likely have been more appropriate. There is potential risk of bias from industry involvement in all aspects of the study process.

Clinical Safety:
Clascoterone cream had a similar overall rate of treatment emergent adverse events (TEAE) compared to vehicle (11.3% and 11.4% vs. 11.5% and 13.8%)(**Table 4**).[3] LSR were reported separately from TEAE and were similar between clascoterone and placebo (**Table 2**).[43] In a 9-month open label extension study, the overall frequency of any LSR remained similar rather than dissipating with time.[47] Pregnant women were excluded from these studies. Animal data using supratherapeutic systemic doses of clascoterone show higher rates of malformations and pregnancy loss.[43,45,46] Safety in pregnancy in unknown. Systemic absorption following 14 days of topical application of clascoterone has resulted in HPA axis suppression in 5% of adults and 9% of adolescents (**Table 3**).[43] Long-term risks associated with HPA axis suppression from clascoterone, particularly in the adolescent population, are unknown.

Table 2. New or Worsening Local Skin Reactions[43]

	Clascoterone 1% cream N=674	**Vehicle cream N=656**
Edema	24 (3.6%)	23 (3.5%)
Erythema	82 (12.2%)	101 (15.4%)
Pruritis	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%)

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Acne severity
2) Number of inflammatory lesions
3) Number of non-inflammatory lesions
4) Quality of Life
5) Serious adverse events

Primary Study Endpoint:
1) IGA reduction (severity)
2) Reduction in inflammatory lesions
3) Reduction in non-inflammatory lesions

6) Study withdrawal due to an adverse event

Table 3. Pharmacology and Pharmacokinetic Properties.[43]

Parameter	
Mechanism of Action	• Androgen receptor inhibitor • Exact mechanism for treatment of acne vulgaris is unknown
Systemic absorption	• Steady state achieved by day 5 • Day 14 Mean ± SD maximum plasma concentration 4.5 ± 2.9 ng/mL • Day 14 HPA axis suppression observed in 5% (1/20) of adults and 9% (2/22) of adolescents. All returned to normal 4 weeks after end of treatment
Distribution and Protein Binding	84% to 89% plasma protein binding
Elimination	• Primary metabolite cortexolone with other possible unidentified metabolites • Excretion not fully characterized
Half-Life	Not reported
Metabolism	Low level inhibition of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 with no expected effect on other substrates

Abbreviations: CYP = cytochrome p450 enzymes; HPA = Hypothalamic-Pituitary-Adrenal; SD = Standard deviation

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Study 1 NCT 02608450[3,44,45] CB-03-01/25 Phase 3, DB, VC, RCT	1. Clascoterone 1% cream twice daily x 12 weeks 2. Vehicle cream twice daily x 12 weeks Randomized 1:1 Visit at baseline, week 4, week 8, and week 12. Open-label extension planned for additional 9 months	<u>Demographics</u>: Male: 38.4% Median age: 18.0 years Race White: 84.0% Black: 9.7% Asian: 2.7% Fitzpatrick skin type Type I: 2.0% Type II: 31.4% Type III: 34.3% Type IV: 17.9% Type V: 7.1% Type VI: 7.3% Baseline IGA 3 (moderate): 82.3% 4 (severe): 17.7% TLC [mean (SD)] 1. 101.5 (25.12) 2. 103.6 (26.13) NILC [mean (SD)] 1. 59.1 (22.19) 2. 60.7 (22.09) ILC [mean (SD)] 1. 42.4 (11.77) 2. 42.9 (12.31) <u>Key Inclusion Criteria</u>: -Male and non-pregnant females -9 years or older -Moderate to Severe facial acne vulgaris (IGA grade 3 or 4) -30 to 75 ILC -30 to 100 NILC -consistent skincare program 1 month prior to enrollment & for duration of study <u>Key Exclusion Criteria</u>: -more than 2 facial nodules -nodulocystic acne -current use of any OTC or Rx topical (facial) or systemic antiacne product	<u>ITT</u>: 1. 353 2. 355 <u>PP:</u> 1. 270 2. 260 <u>Attrition</u>: 1. 66 (18.7%) 2. 65 (18.3%)	<u>Primary Endpoint</u>: Treatment success: ≥2 point IGA reduction AND score of 0 or 1 (week 12) 1. 57 (16.1%) 2. 25 (7.0%) Point estimate 2.3 (95% CI, 1.4 to 3.8) P<0.001 Treatment success adjusted proportions for missing data: 1. 18.4% 2. 9.0% Change in NILC (baseline to week 12) 1. -19.4 2. -13.0 Difference -6.4 (95% CI -10.3 to -2.6) P<0.001 Change in ILC (baseline to week 12) 1. -19.3 2. -15.5 Difference -3.8 (95% CI -6.4 to -1.3) P<0.003 <u>Secondary Endpoints</u>: Change in TLC (baseline to week 12) 1. -39.1 2. -28.8 Difference -10.3 (95% CI -15.7 to -4.9) P<0.001	9.1% /11	<u>Outcome</u> TEAE : 1. 40 (11.3%) 2. 41 (11.5%) Severe TEAE: 1. 0 2. 2 (0.6%) Study discontinuation due to TEAE: 1. 3 (0.8%) 2. 4 (1.1%) Most frequent TEAE: Nasopharyngitis 1. 6 (1.7%) 2. 13 (3.7%) Headache 1. 2 (0.6%) 2. 1 (0.3%) Oropharyngeal pain 1. 2 (0.6%) 2. 1 (0.3%) Vomiting 1. 2 (0.6%) 2. 2 (0.6%)	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (low) randomization via Datatrak One software, permuted block design, block size 4. Blinding of clinical team, patients, investigators, monitors, employees of study site. <u>Performance Bias</u>: (low) Vehicle cream identical to active cream in color, consistency, and smell. Both were packaged in identical blinded tubes. <u>Detection Bias</u>: (low) Lesion count, IGE, adverse events, and LSR assessed at each visit by same investigator (when possible). <u>Attrition Bias</u>: (low) Missing primary endpoint data imputation by: multiple imputation using missing at random assumption, missing at worst value (for entire set), worst case, LOCF, and baseline observation carried forward. Large number LTFU in both groups. <u>Reporting Bias</u>: (low) Roughly ½ of attrition was for "withdrawal" without reason stated. LSR not presented in safety results table. <u>Other Bias:</u> (high) Industry sponsor Cassiopea SpA responsible for funding, preparation, review, approval, and publication submission of manuscript and study collection, management, analysis, data interpretation. **Applicability**: <u>Patient</u>: Patients predominantly white and with Fitzpatrick skin type II or III (of VI), limiting applicability to other skin types (e.g. African Americans or Latinos). Only 18% had severe acne. <u>Intervention</u>: Intervention appropriate with consistent skincare routine. <u>Comparator</u>: Placebo appropriate, but comparison with active comparator would enable comparative assessment of clinical efficacy. <u>Outcomes</u>: IGA and lesion count are common outcomes in acne assessment.

		-women on COC for non-acne indications must be on tx x 12 weeks prior to study and remain on same product & dose throughout -Systemic CS not allowed within 4 weeks, non-systemic CS (inhaled, intranasal, ocular) require stable dose x 4 weeks -light treatments, microdermabrasion, or chemical peels within 8 weeks						<u>Setting</u>: 45 sites in US, 7 sites in Ukraine, 3 sites in Republic of Georgia
2. Study 2 NCT 02608476[3,44,46] CB-03-01/26 Phase 3, DB, VC, RCT	See Study 1	<u>Demographics</u>: Male: 36.6% Median age: 18.0 years Race White: 96.3% Black: 1.8% Asian: 0.5% Fitzpatrick skin type Type I: 2.6% Type II: 31.3% Type III: 45.9% Type IV: 15.2% Type V: 3.8% Type VI: 1.2% Baseline IGA 3 (moderate): 84.4% 4 (severe): 15.6% TLC [mean (SD)] 1. 105.7 (25.76) 2. 104.6 (24.18) NILC [mean (SD)] 1. 62.8 (21.37) 2. 63.3 (20.52) ILC [mean (SD)] 1. 42.9 (12.20) 2. 41.3 (10.96) <u>Key Inclusion Criteria</u>: See Study 1 <u>Key Exclusion Criteria</u>: See Study 1	<u>ITT</u>: 1. 369 2. 363 <u>PP:</u> 1. 286 2. 268 <u>Attrition</u>: 1. 67 (18.2%) 2. 81 (22.3%)	<u>Primary Endpoint</u>: Treatment success: ≥2 point IGA reduction AND score of 0 or 1 (week 12) 1. 69 (18.7%) 2. 17 (4.7%) Point estimate 3.7 (95% CI, 2.2 to 6.3) P<0.001 Treatment success adjusted proportions for missing data: 1. 20.3% 2. 6.5% Change in NILC (baseline to week 12) 1. -19.4 2. -10.8 Difference -8.6 (95% CI -12.3 to -4.9) P<0.001 Change in ILC (baseline to week 12) 1. -20.0 2. -12.6 Difference -7.4 (95% CI -9.8 to -5.1) P<0.001 <u>Secondary Endpoints</u>: Change in TLC (baseline to week 12)	14%/ 8	TEAE: 1. 42 (11.4%) 2. 50 (13.8%) Severe TEAE: 1. 0 2. 1 (0.3%) Study discontinuation due to TEAE: 1. 2 (0.5%) 2. 8 (2.2%) Most frequent TEAE: Nasopharyngitis 1. 4 (1.1%) 2. 7 (1.9%) Headache 1. 4 (1.1%) 2. 3 (0.8%) Oropharyngeal pain 1. 4 (1.1%) 2. 4 (1.1%) Vomiting 1. 2 (0.5%) 2. 1 (0.3%)	NA	**Risk of Bias (low/high/unclear)**: See study 1 **Applicability**: <u>Patient</u>: See study 1 <u>Intervention</u>: See study 1 <u>Comparator</u>: See study 1 <u>Outcomes</u>: See study 1 <u>Setting</u>: 10 sites in US, 8 sites in Bulgaria, 9 sites in Romania, 12 sites in Poland, 3 sites in Serbia, 6 sites in Republic of Georgia

				1. -40.0 2. -23.6 Difference -16.4 (95% CI -21.8 to -11.0) P<0.001				

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; COC = combined oral contraceptives; CS = corticosteroids; DB = double-blind; IGA = Investigator's Global assessment; ILC = inflammatory lesion count; ITT = intention to treat; LOCF = last observation carried forward; LSR = local skin reaction; LTFU = lost to follow-up; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NILC = non-inflammatory lesion count; NNH = number needed to harm; NNT = number needed to treat; OTC = over-the-counter; PP = per protocol; RCT = randomized controlled trial; Rx = prescription; SD = standard deviation; TEAE = treatment emergent adverse event; TLC = total lesion count; tx = treatment; US = United States; VC = vehicle-controlled

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Generic	Brand	Route	Form	PDL
adapalene	ADAPALENE	TOPICAL	CREAM (G)	Y
adapalene	DIFFERIN	TOPICAL	CREAM (G)	Y
adapalene	ADAPALENE	TOPICAL	GEL (GRAM)	Y
adapalene	DIFFERIN	TOPICAL	GEL (GRAM)	Y
adapalene	ADAPALENE	TOPICAL	GEL W/PUMP	Y
adapalene	DIFFERIN	TOPICAL	GEL W/PUMP	Y
adapalene	DIFFERIN	TOPICAL	LOTION	Y
adapalene/benzoyl peroxide	ADAPALENE-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	Y
adapalene/benzoyl peroxide	EPIDUO	TOPICAL	GEL W/PUMP	Y
azelaic acid	AZELAIC ACID	TOPICAL	GEL (GRAM)	Y
azelaic acid	FINACEA	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	CLEANSER	Y
benzoyl peroxide	PANOXYL	TOPICAL	CLEANSER	Y
benzoyl peroxide	BENZEFOAM	TOPICAL	FOAM	Y
benzoyl peroxide	ACNE MEDICATION	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZAC W 10	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZAC W 2.5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZAC W 5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	PANOXYL AQ 2.5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	PANOXYL AQ 5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BPO	TOPICAL	TOWELETTE	Y
clindamycin phos/benzoyl perox	BENZACLIN	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	NEUAC	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	ACANYA	TOPICAL	GEL W/PUMP	Y
clindamycin phos/benzoyl perox	BENZACLIN	TOPICAL	GEL W/PUMP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	TOPICAL	GEL W/PUMP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	FOAM	Y
clindamycin phosphate	EVOCLIN	TOPICAL	FOAM	Y
clindamycin phosphate	CLEOCIN T	TOPICAL	GEL (GRAM)	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	GEL (GRAM)	Y
clindamycin phosphate	CLEOCIN T	TOPICAL	LOTION	Y

clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	LOTION	Y
clindamycin phosphate	CLINDACIN ETZ	TOPICAL	MED. SWAB	Y
clindamycin phosphate	CLINDACIN P	TOPICAL	MED. SWAB	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	MED. SWAB	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	SOLUTION	Y
clindamycin/tretinoin	CLINDAMYCIN PHOS-TRETINOIN	TOPICAL	GEL (GRAM)	Y
clindamycin/tretinoin	ZIANA	TOPICAL	GEL (GRAM)	Y
dapsone	ACZONE	TOPICAL	GEL (GRAM)	Y
dapsone	DAPSONE	TOPICAL	GEL (GRAM)	Y
erythromycin base in ethanol	ERYGEL	TOPICAL	GEL (GRAM)	Y
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	GEL (GRAM)	Y
erythromycin base in ethanol	ERY	TOPICAL	MED. SWAB	Y
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	MED. SWAB	Y
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	SOLUTION	Y
isotretinoin	ABSORICA	ORAL	CAPSULE	Y
isotretinoin	AMNESTEEM	ORAL	CAPSULE	Y
isotretinoin	CLARAVIS	ORAL	CAPSULE	Y
isotretinoin	ISOTRETINOIN	ORAL	CAPSULE	Y
isotretinoin	MYORISAN	ORAL	CAPSULE	Y
isotretinoin	ZENATANE	ORAL	CAPSULE	Y
sulfacetamide sodium	KLARON	TOPICAL	SUSPENSION	Y
sulfacetamide sodium	SULFACETAMIDE SODIUM	TOPICAL	SUSPENSION	Y
tretinoin	AVITA	TOPICAL	CREAM (G)	Y
tretinoin	RETIN-A	TOPICAL	CREAM (G)	Y
tretinoin	TRETINOIN	TOPICAL	CREAM (G)	Y
tretinoin	ATRALIN	TOPICAL	GEL (GRAM)	Y
tretinoin	AVITA	TOPICAL	GEL (GRAM)	Y
tretinoin	RETIN-A	TOPICAL	GEL (GRAM)	Y
tretinoin	TRETINOIN	TOPICAL	GEL (GRAM)	Y
tretinoin microspheres	RETIN-A MICRO	TOPICAL	GEL (GRAM)	Y
tretinoin microspheres	TRETINOIN MICROSPHERE	TOPICAL	GEL (GRAM)	Y
tretinoin microspheres	RETIN-A MICRO PUMP	TOPICAL	GEL W/PUMP	Y
tretinoin microspheres	TRETINOIN MICROSPHERE	TOPICAL	GEL W/PUMP	Y
adapalene	PLIXDA	TOPICAL	MED. SWAB	N
adapalene	ADAPALENE	TOPICAL	SOLUTION	N
adapalene/benzoyl peroxide	EPIDUO FORTE	TOPICAL	GEL W/PUMP	N
azelaic acid	AZELEX	TOPICAL	CREAM (G)	N
azelaic acid	FINEVIN	TOPICAL	CREAM (G)	N
azelaic acid	FINACEA	TOPICAL	FOAM	N
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	CLEANSER	N

benzoyl peroxide	PANOXYL-4	TOPICAL	CLEANSER	N
clindamycin phos/benzoyl perox	ONEXTON	TOPICAL	GEL (GRAM)	N
clindamycin phos/benzoyl perox	ONEXTON	TOPICAL	GEL W/PUMP	N
clindamycin phos/skin clnsr 19	CLINDACIN ETZ	TOPICAL	KIT	N
clindamycin phos/skin clnsr 19	CLINDACIN PAC	TOPICAL	KIT	N
clindamycin phosphate	CLINDAGEL	TOPICAL	GEL DAILY	N
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	GEL DAILY	N
clindamycin/benzoyl/emol cmb94	NEUAC	TOPICAL	CMB CR GEL	N
dapsone	ACZONE	TOPICAL	GEL W/PUMP	N
dapsone	DAPSONE	TOPICAL	GEL W/PUMP	N
erythromycin/benzoyl peroxide	AKTIPAK	TOPICAL	GEL (EA)	N
erythromycin/benzoyl peroxide	BENZAMYCIN	TOPICAL	GEL (GRAM)	N
erythromycin/benzoyl peroxide	ERYTHROMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	N
isotretinoin	ABSORICA	ORAL	CAPSULE	N
isotretinoin, micronized	ABSORICA LD	ORAL	CAPSULE	N
tazarotene	FABIOR	TOPICAL	FOAM	N
tazarotene	ARAZLO	TOPICAL	LOTION	N
tretinoin	TRETIN-X	TOPICAL	CREAM (G)	N
tretinoin	ALTRENO	TOPICAL	LOTION	N
tretinoin microspheres	RETIN-A MICRO PUMP	TOPICAL	GEL W/PUMP	N
tretinoin/emol 9/skin cleansr1	TRETIN-X	TOPICAL	COMBO. PKG	N
trifarotene	AKLIEF	TOPICAL	CREAM (G)	N
benzoyl peroxide	ACNE MEDICATION	TOPICAL	LOTION	
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	LOTION	

Appendix 2: Abstracts of Comparative Clinical Trials
n/a

Appendix 3: Medline Search Strategy

1	Adapalene/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	32
2	azelaic acid.mp.	759
3	Benzoyl Peroxide/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	633
4	Clindamycin/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	3295
5	Dapsone/ae, th, to [Adverse Effects, Therapy, Toxicity]	849
6	Erythromycin/ae, tu, th, to [Adverse Effects, Therapeutic Use, Therapy, Toxicity]	5145
7	Isotretinoin/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	2133
8	Sulfacetamide/ae, tu, th, to [Adverse Effects, Therapeutic Use, Therapy, Toxicity]	123
9	Tretinoin/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	4923
10	Adapalene, Benzoyl Peroxide Drug Combination/ or Adapalene/	388
11	tazarotene.mp.	603
12	trifarotene.mp.	19
13	Contraceptives, Oral/ae, tu, th, to [Adverse Effects, Therapeutic Use, Therapy, Toxicity]	9731
14	Acne Vulgaris/	11742
15	Acne Conglobata/	20
16	acne fulminans.mp.	186
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	27658
18	14 or 15 or 16	11798
19	17 and 18	2486
20	limit 19 to (english language and (adaptive clinical trial or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review"))	659
21	limit 20 to yr="2019 -Current"	29
22	Clascoterone.mp.	13
23	CB-03-01.mp.	6
24	22 or 23	13
25	20 and 24	1

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WINLEVI Cream safely and effectively. See full prescribing information for WINLEVI Cream.

WINLEVI® (clascoterone) cream, for topical use
Initial U.S. Approval: 2020

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. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening). Avoid contact with eyes, mouth, and mucous membranes. (2)
- Not for ophthalmic, oral or vaginal use. (2)

DOSAGE FORM AND STRENGTHS

Cream 1%. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Local Irritation: Pruritus, burning, skin redness or peeling may be experienced with WINLEVI cream. If these effects occur, discontinue or reduce the frequency of application of WINLEVI cream. (5.1)
- Hypothalamic-pituitary-adrenal (HPA) axis suppression may occur during or after treatment with clascoterone. (5.2)
- Attempt to withdraw use if HPA axis suppression develops. (5.2)
- Pediatric patients may be more susceptible to systemic toxicity. (5.2, 8.4)
- Hyperkalemia: Elevated potassium levels were observed in some subjects during the clinical trials. (12.2)

ADVERSE REACTIONS

Most common adverse reactions occurring in 7 to 12% of patients are erythema/reddening, pruritus and scaling/dryness. Additionally, edema, stinging, and burning occurred in >3% of patients and were reported in a similar percentage of subjects treated with vehicle. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cassiopea at 1-855-WINLEVI or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2020

Appendix 5: Key Inclusion Criteria

Population	Adults and children with acne conglablata, acne fulminans, or severe acne vulgaris
Intervention	Clascoterone topical therapy, other acne therapies (see **appendix 3**), spironolactone, oral contraceptives
Comparator	Placebo or active treatment
Outcomes	Inflammatory and noninflammatory lesion reduction, adverse reactions
Timing	Not applicable
Setting	Outpatient therapy

Acne Medications

Goal(s):
- Ensure that medications for acne are used appropriately for OHP-funded conditions.

Length of Authorization:
- Up to 12 months

Requires PA:
- All drugs in the Acne medications class

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class and process appropriate PA.	**No:** Approve for 12 months.

P&T/DUR Review: 02/21 (SF); 06/2020 (SF); 11/18 (JP)
Implementation: 7/1/20; 1/1/1