Clascoterone (WINLEVI) Cream
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- First-in-class androgen receptor inhibitor structurally similar to dihydrotestosterone and spironolactone.
- The exact mechanism by which topical clascoterone reduces acne is unknown. In vitro studies suggest that it binds to the androgen receptor within sebocytes and reduces the effect of dihydrotestosterone (DHT) on gene transcription involved in sebum production and inflammation.
- [1]
- Clascoterone is also referred to as cortexolone 17α-propionate and CB-03-01.

Indications Under Review in This Document

- Topical treatment of acne vulgaris in patients 12 years of age and older.[2]

Dosage Form Under Review

- Cream 1%, available in 60-g tubes

Clinical Evidence Summary

Efficacy Considerations

- An active- and vehicle-controlled phase 2 randomized clinical trial (RCT) suggested that clascoterone was similar to topical tretinoin in efficacy in the treatment of mild to moderate facial acne.[3]
- Two vehicle-controlled phase 3 RCTs established the efficacy of clascoterone in the treatment of moderate to severe facial acne for up to 12 weeks.[1,4]
- Supportive trials included an open-label phase 2a pharmacokinetic and safety / tolerability study in patients with moderate to severe acne on the face, chest, and/or back[5] and a vehicle-controlled, phase 2b, dose escalation RCT that compared different concentrations of clascoterone cream (0.1%, 0.5%, and 1%) in patients with facial acne. The phase 2b RCT determined that the 1% formulation was the best candidate for further product development.[6]

Clinical Trials

Phase 2 Tretinoin- and Vehicle-controlled Clinical Trial

- An 8-week, phase 2, multicenter, double-blind, placebo-controlled pilot RCT in Romania compared clascoterone cream 1% with tretinoin cream 0.05% and placebo cream (all constituted with the same excipients as clascoterone cream) in 77 adult males with mild to moderate facial acne vulgaris (IGA score of

2 or 3).[3] IGA success in this trial was defined differently from the later phase 3 trials as grade of 0 or 1 for patients who had a baseline IGA score of 3, and grade 0 for those who had a baseline score of 2. This study supported the rationale to use topical antiandrogens for acne (and to proceed with larger phase 3 trials) and was the only active-controlled trial available.

- A nonsignificantly higher percentage of patients on clascoterone than tretinoin and placebo achieved IGA success: 6/27 (22%) vs 3/26 (12%) and 1/14 (7%), respectively. Clascoterone was statistically superior to placebo and numerically (nonsignificantly) better than tretinoin in both total lesion count and acne severity index. Clascoterone was significantly better than tretinoin and placebo in inflammatory lesion count (ILC).
- Clascoterone had significantly lower irritancy scores than placebo at Week 2 but showed no significant differences thereafter. Irritancy scores decreased over time and were consistently numerically lower with clascoterone than tretinoin (range of mean scores from Week 2 to Week 8: 1.29 to 0.30 vs 2.20 to 0.62, respectively). Placebo patients (3/14, 21%) had a numerically higher rate of adverse events than clascoterone (3/28, 11%) and tretinoin (2/30, 7%).

Phase 3 Vehicle-controlled Clinical Trials

- Clascoterone cream was shown to be efficacious in 1421 evaluated patients with moderate to severe facial acne vulgaris in Study CB-03-01/25 (Study 25) and CB-03-01/26 (Study 26), two identically designed, 12-week, phase 3, multinational, multicenter, double-blind, vehicle-controlled randomized clinical trials (RCTs).[1,4]
  - **Entry criteria**: Study patients had to be ≥ 9 years old, be on a skin care program, and have moderate or severe facial acne vulgaris on the Investigator's Global Assessment scale (score of 3 or 4), 30 to 75 inflammatory lesions (papules, pustules and nodules), 30 to 100 noninflammatory lesions (open and closed comedones), and no more than two facial nodules. Patients were ineligible if topical anti-acne treatments had been used within the previous 2 weeks; retinoids within the previous 4 weeks; light treatments, microdermabrasion, or chemical peels within the previous 8 weeks; systemic corticosteroids (including intramuscular and intralesional injections) or antibiotics within the previous 4 weeks; spironolactone within the previous 8 weeks; or retinoids within the previous 6 months.
  - **Patient characteristics at baseline**: 55% adults (≥ 18 years), mean age 20 years; age range 9 to 58 years; 38% male, 41% US, 91% Caucasian, 83% moderate acne (IGA score of 3), mean ILC 42.4, and mean noninflammatory lesion count (NILC) 61.4.
  - **Primary efficacy measures**: IGA success, defined as ≥ 2-point reduction in IGA from baseline and a score of 0 (clear) or 1 (almost clear); and reduction from baseline in ILC and NILC.
  - **Results:** Efficacy data for the two phase 3 RCTs are summarized in Table 1.

Table 1 Week-12 efficacy results from phase 3 RCTs (FDA ITT analysis)

Outcome Measure	Study	Clascoterone Cream	Vehicle Cream	Relative Risk (95% CL)	Absolute Diff (95% CL)	NNT (95% CI)	Q
IGA Success, n/N (%)[†]	25	66/353 (18.8)	31/355 (8.6)	2.1 (1.4, 3.2)	9.9 (4.0, 15.7)	11 (7, 21)	M[α]
	26	77/369 (20.8)	24/363 (6.5)	3.2 (2.0, 4.9)	14.3 (8.9, 19.7)	8 (6, 11)	
	Pooled	143/722 (19.8)	54/718 (7.5)	2.6 (2.0, 3.5)	12.3 (8.8, 15.8)	9 (7, 12)	
RFB in ILC, no. of lesions (% RFB)	25	20.4 (32.6)	13.0 (21.8)	—	7.3 (3.5, 11.1)	—	H
	26	19.5 (29.6)	10.8 (15.7)	—	8.7 (4.5, 12.4)	—	
RFB in NILC, no. of lesions (% RFB)	25	19.3 (44.6)	15.4 (36.3)	—	3.9 (1.3, 6.5)	—	H
	26	20.1 (47.1)	12.6 (29.7)	—	7.5 (5.2, 9.9)	—	

Sources: 1

IGA success, Investigator's global assessment success, defined as ≥2-point reduction from baseline and a score of 0 (clear) or 1 (almost clear); ILC, Inflammatory lesion count; NILC, Noninflammatory lesion count (e.g., comedones); Q, GRADE quality of evidence; RFB, Reduction from baseline

[†] Adjusted proportions

[α] Unclear risk of bias (incomplete information). Downgraded for imprecision (<300 events).

- Clascoterone cream showed small to negligible short-term (12-week) benefits, with about 20% of patients achieving IGA success and reductions of less than 10 in ILC and less than 8 in NILC relative to vehicle.
- The anticipated absolute effect for achieving IGA success in 12 weeks was 120 (95% CI 75 to 188) more per 1000 patients.
- **Clinical Outcomes**: None were evaluated.
- **Durability of Response**: Not evaluated.
- **Recurrence Rate**: Not evaluated.
- **Subgroup Response Predictors**: None were clearly identified.[1]

Network Meta-analyses

- None that included clascoterone were found.

Safety Considerations

- **Boxed Warnings**: None.
- **Contraindications**: None.
- **Other Warnings / Precautions**:
  - **Local skin reactions**
  - **Hypothalamic-pituitary-adrenal (HPA) axis suppression** occurred in 1 (5%) of 20 evaluated adults.[1] The incidence of HPA axis suppression was higher in younger patients, with 2 (9%) of 22 adolescents and 4 (15%) of pediatric patients (9–11 years old) developing HPA axis suppression in two phase 2 maximal use pharmacokinetic studies.[1]
- **Deaths and Serious Adverse Events**: In the two phase 3 RCTs, no patients on clascoterone and 2 patients (0.3%) on vehicle reported serious treatment-emergent adverse events (TEAEs).[1] There were no deaths.
- **Withdrawals due to Adverse Events**: There were 5 patients (0.7%) on clascoterone and 12 patients (1.7%) on vehicle who withdrew from therapy because of TEAEs.[1] There was no apparent trend in the types of adverse events leading to withdrawal from clascoterone.
- **Common Adverse Events**: Nasopharyngitis occurred in 12 clascoterone patients (1.7%) and 20 vehicle patients (3.5%) in the two phase 3 RCTs. Local skin reactions occurred at similar rates in the treatment and vehicle groups. Adverse events reported by ≥ 1% of patients and at a higher incidence than with vehicle were edema, scaling / dryness, and striae rubrae. Most adverse events were mild to moderate in intensity.[1] No systemic adverse events occurred in the two phase 3 RCTs.[4]

- **Adverse Events with Long-term Exposure**: Study CB-03-01/27 (Study 27) was a 9-month, phase 3, multinational, multicenter, open-label long-term extension of the two phase 3 RCTs.[1,7] Study 27 evaluated the safety of clascoterone cream (applied twice daily for up to 9 months to the face or trunk) in 607 evaluated patients and showed acceptable safety and tolerability. However, 90 patients (14.8%) were lost to follow-up. Of 123 patients who remained on clascoterone therapy for 12 months (3 months in the RCT plus 9 months in the extension study), 19 patients (7.3%) reported ≥ 1 TEAE and no patients reported a treatment-related serious TEAE or withdrawal TEAEs.[1] Moderate depigmentation of hair in the facial treatment area occurred in one patient, was deemed to be possible related to study drug, and led to treatment discontinuation.[7]
- **Adverse Events of Special Interest**: Hyperkalemia, gynecomastia and menstrual irregularities were of specific interest because of the structural similarity of clascoterone to spironolactone.
    - **Hyperkalemia**. A shift in potassium concentrations from low or normal to high (> 5.0 mmol/L) occurred in 26 (5.3%) of 488 clascoterone-treated patients and 4 (3.9%) of 103 placebo-treated patients.[1] The risk difference was 1.4% (95% CI, –2.8% to 5.7%).
        - Among the adult (≥ 18 years) age group, the corresponding rates were 12 (3.9%) of 311 clascoterone patients and 2 (3.0%) of 66 vehicle patients.
        - The maximum mean (SD) percentage change from baseline in potassium concentration was 0.2% (11.5) in 495 clascoterone-treated patients and 0.3% (10.3) in 103 vehicle-treated patients.
    - **Gynecomastia**. There was no increased risk of gynecomastia in the 12-week phase 3 RCTs.
    - **Polycystic Ovaries / Amenorrhea**. In the long-term observational clascoterone safety study (Study 27), 3 patients developed polycystic ovaries and 1 patient developed amenorrhea.
- **Pregnancy**: No data in pregnant women. Teratogenic in animals.
- **Lactation**: No human data.
- **Geriatric Use**: Insufficient data.

Other Considerations

- **Storage**
    - **Pharmacy Storage**: Refrigerate between 36°F and 46°F (2°C and 8°C).
    - **Storage after Dispensing**: Room temperature between 68°F and 77°F (20°C and 25°C). Do not freeze. Discard unused product 180 days after the date of dispensing or 1 month after first opening, whichever is sooner.
- **Pharmacokinetics**: Systemic exposure following topical clascoterone application seems to be very low. Plasma concentrations of clascoterone and cortexolone, a possible primary metabolite, were detectable after topical administration of clascoterone cream (mean dose 6 g twice daily) for 2 weeks in 20 adults with moderate to severe acne vulgaris.[2] Excretion of clascoterone has not been fully characterized in humans.
    - **Clascoterone**: C_{max} (± SD) 4.5 (2.9) ng/mL, AUC_t 37.1 (22.3) h·ng/mL, C_{avg} 3.1 (1.9) ng/mL.
    - **Cortexolone**: Plasma concentrations were generally below or near 0.5 ng/mL (the lower limit of quantitation).
- **Drug Interactions**: No clinical studies available. In vitro studies suggest that clascoterone has no clinically meaningful effects on the pharmacokinetics of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.
- **Age-related Efficacy and Risks of HPA Axis Suppression and Hyperkalemia**. Clascoterone cream was not approved in children 9 to 11 years of age because of a lack of efficacy in that age subgroup and increased risks of HPA axis suppression (10%) and hyperkalemia (33.3%).[1] Interestingly, steady-state trough concentrations of clascosterone in pediatric patients were generally *lower* than those in adults and adolescents (~0.6 ng/mL vs ~2 ng/mL, respectively).[1] AUC data was not available in pediatric patients.

Exploratory FDA exposure-response analyses showed no correlation between systemic exposure under maximal use conditions and incidence of hyperkalemia. No exposure-response data was reported for incidence of HPA suppression.

Other Therapeutic Options

- Topical treatment options include topical benzoyl peroxide, retinoids, antibiotics and other agents.
- Systemic options include antibiotics (tetracyclines preferred), isotretinoin and, in females, antiandrogenic hormonal therapy.
- Topical treatments for acne vulgaris are summarized in Table 2.

Table 2 Topical Treatments for Acne Vulgaris

Drug	Formulation(s)	Formulary*	Safety Considerations	Other Considerations
Antiandrogen				
Clascoterone	**Cream**	TBD	Local skin reactions; HPA axis suppression Pregnancy / Lactation: No human data.	Occlusive dressings, wide application or prolonged use can increase absorption. No study patients were over 58 yrs old. Requires refrigeration in pharmacy. Expires 1 month after opening.
Retinoids				
Adapalene	Cream Gel Lotion Solution Swab	No Yes No No No	Photosensitivity, skin irritation. Pregnancy Risk Factor: C. Other topical agents are preferred. Contraindicated in pregnancy in Canada.	Not oxidized by BPO. Less irritating than first-generation topical retinoids. Adapalene-based regimens have the most evidence as maintenance therapy. Gel 0.1% is available OTC.
Tazarotene	Cream Foam Gel Lotion	No No No No	CI: Pregnancy. Fetal risk Local irritation Photosensitivity Sunburn risk Flammable	Tazarotene gel 0.1% was superior to adapalene gel 0.1%,[8,9] but monotherapy with adapalene gel 0.3% was noninferior to tazarotene gel 0.1%.[10] Tazarotene cream 0.1% was superior to tretinoin gel 0.025%.[11] Gel and cream are also approved for psoriasis. Not oxidized by BPO.
Tretinoin	Cream (including PPP-2†) Gel (including micronized and PPP-2†) Liquid Lotion Microsphere gel†	Yes Yes No No No	CI: hypersensitivity. Avoid use during pregnancy, especially first trimester; however, fetal risk appears to be low. Fish allergies (with ATRALIN micronized gel) Photosensitivity Skin irritation	Loses effectiveness by oxidation if administered with BPO. Micronized and microsphere gels lack this interaction. Optimized vehicles† reduce skin irritation.
Trifarotene	Cream	No	No CI. Contraindicated in pregnancy in Canada. Photosensitivity Skin irritation	No active-comparator trials to inform place in therapy.

Drug	Formulation(s)	Formulary*	Safety Considerations	Other Considerations
Antimicrobial				
Benzoyl peroxide (BPO)	Bar Cream Foam Gel Liquid (including wash) Lotion Lotion, cleansing Swab Wash (Soap / Detergent)	No No No Yes Yes Yes No No No	Concentration-dependent local skin irritation; should not be used in patients with very sensitive skin. Sunscreen protection is recommended.	Considered the preferred topical antimicrobial agent.[12] Avoid monotherapy, but no reports of bacterial resistance. Less effective for microcomedones and NILC than ILC. Adherence can be limited by skin irritation and bleaching of hair and fabrics.
Antibiotics				
Clindamycin	Foam Gel Lotion Solution Swab	No No Yes Yes Yes	Rare pseudo-membranous colitis Eye irritation with solution (contains alcohol) or foam Bacterial resistance (monotherapy)	Generally the preferred topical antibiotic but should not be used as monotherapy. Combine with BPO or topical retinoid to reduce bacterial resistance.[13]
Dapsone	Gel	No	Cases of methemoglobinemia Hemolysis in G6PD deficiency	Reversible yellow-orange skin discoloration when applied with BPO.
Erythromycin	Gel Pad Pledget Solution Solution 1.5% Solution 2% Swab	Yes No No No Yes No	Local skin irritation Superinfection Pseudomembranous colitis Bacterial resistance (monotherapy)	Reduced efficacy due to bacterial resistance has led to decrease in use (clindamycin preferred). Combine with BPO to reduce bacterial resistance.
Minocycline	Foam 4%	No	Headache Bacterial resistance (monotherapy)	LASA confusion with minocycline foam 1.5% for rosacea. Combine with BPO to reduce bacterial resistance.
Fixed Combination Products				
BPO / Adapalene	Gel	No	Local skin irritation	BPO bleaches hair and fabrics. Retinoid is anti-microcomedogenic. BPO 2.5% / Adapalene 0.3% gel was shown to be efficacious for moderate to severe inflammatory non-nodulocystic acne (w/o systemic agent).[14]
BPO / Clindamycin	Gel	No	Local skin irritation	BPO bleaches hair and fabrics Better than BPO and clindamycin monotherapies.[15]
BPO / Erythromycin	Gel Gel Packet / Kit (for compounding)	Yes No	Local skin irritation	BPO bleaches hair and fabrics.
BPO / Salicylic acid	Pad	No	Local skin irritation	BPO bleaches hair and fabrics. Available OTC. BPO / salicylic acid is superior to topical BPO, clindamycin, and BPO / clindamycin.[15]
Clindamycin / Tretinoin	Gel	No	Colitis Photosensitivity Local skin irritation	Anti-microcomedogenic, anti-seborrheic, antiinflammatory. Does not bleach hair and fabrics.
	Cream Lotion	No Yes	CI in sulfa hypersensitivity and renal disease	No FDA-approved products.

Drug	Formulation(s)	Formulary*	Safety Considerations	Other Considerations
Sodium Sulfacetamide / Sulfur	Pad Suspension Wash	No No No	Rare, severe autoimmune reactions, blood dyscrasias, dermatologic reactions, hepatic injury Pregnancy category C	Can be useful for treatment of concurrent acne and rosacea and/or seborrheic dermatitis.
Other				
Azelaic acid	Cream Foam Gel	No No No	Local skin irritation (itching, burning, stinging) Depigmentation	Antimicrobial and anti-microcomedogenic Similar to adapalene in maintaining lesion clearance.[13] Useful in pregnant women and PIH.
Salicylic acid	Bar Pad	No No	Local skin irritation	Keratolytic and anti-microcomedogenic Considered to be similar in efficacy to BPO for mild acne but better than BPO in preventing comedones. Available OTC.

Sources: 1,15,16

List may not be all-inclusive.

AAD, American Academy of Dermatology; **BPO**, Benzoyl peroxide; **CI**, Contraindications; **ILC**, Inflammatory lesion count; **NILC**, Noninflammatory lesion count (e.g., comedones); **PIH**, Postinflammatory hyperpigmentation; **PPP-2**, Polyolprepolymer-2; **RFB**, Reduction from baseline; **W/P**, Warnings / Precautions

* None of the formulations have PBM Clinical Guidance

† Optimized tretinoin formulations include polyolprepolymer-2 cream and micronized, microsphere, and polyolprepolymer-2 gel.

‡ Marked nonformulary in the Pharmacy Product System – National.

Projected Place in Therapy

- **Epidemiology of Acne Vulgaris and Prevalence**. The prevalence of acne vulgaris is estimated to be 12% and 26% in men and women 40–49 years of age, respectively, and 7% and 15% in men and women aged ≥ 50 years, respectively.
- **Place in Therapy Based on Medical Society Guidelines**. No society guidelines on acne vulgaris discuss clascoterone. Topical therapies for acne are generally used for mild to moderate acne and can be adjuncts to systemic antibiotics for severe acne.[13,17] Topical retinoid and azelaic acid as single agents are also recommended as maintenance therapy for acne of any severity.[17] Preventing follicular occlusion (i.e., formation of microcomedones) is the primary treatment target; this will interrupt the entire acne cascade.[16] Retinoids, azelaic acid and salicylic acid are the only agents that are anti-microcomedogenic and comedolytic. Antiandrogens primarily reduce sebum production.
- **Potential Place in Therapy Based on the Evidence**. The potential place in therapy of clascoterone cream is uncertain because of limited comparative data. However, it provides another topical anti-acne treatment option in an era of antibiotic stewardship, and could potentially be used as another step in topical therapy before proceeding to systemic antiandrogenic therapy (e.g., low-dose combination oral contraceptives and spironolactone). Clascoterone cream was FDA-approved for the treatment of acne without regard to severity or affected body area. An RCT suggested that clascoterone cream was better than tretinoin cream 0.05% in reducing inflammatory lesion counts and perhaps in tolerability but the trial results were preliminary (phase 2) and unconfirmed. Clascoterone cream 1% was shown in identically designed phase 3 vehicle-controlled RCTs to be efficacious for noninflammatory and inflammatory lesions in the short-term (12 weeks) and adequately safe and tolerated for up to 1 year in the treatment of a predominantly young, female, non-US study population with mostly moderate facial acne. Combination topical therapy or combination topical–systemic therapy with clascoterone cream was not evaluated in clinical trials. No trials compared it against systemic antiandrogenic agents. There is also some uncertainty about the efficacy and

safety of clascoterone cream in US Veteran patients because the study populations were not representative of the VHA population, and therapy longer than 1 year was not evaluated.

- **Potential Place in Therapy in VHA**. Clascoterone cream may be used as an alternative topical treatment option for patients with acne vulgaris who have had an inadequate response or intolerance to two- or three-drug topical combination therapy including benzoyl peroxide, a retinoid and/or antibiotic. Clinicians should be aware that the safety and efficacy of clascoterone cream in combination therapy have not been evaluated. Likewise, the extent of systemic absorption of topically applied clascoterone and the risk of HPA axis suppression in older patients (> 58 years) are unknown. Clinicians should also be aware that clascoterone is structurally similar to spironolactone, and while the risk of hyperkalemia was not increased in study patients ≥ 12 years old, the risk of hyperkalemia has not been determined in actual clinical practice, in elderly patients, or when used concurrently with other drugs that can cause hyperkalemia.

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