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Drug Class Update with New Drug Evaluation: Acne Drugs

Date of Review: June 2020

Date of Last Review: November 2018
Dates of Literature Search: 08/03/2018 - 12/26/2019
Brand Name (Manufacturer): Aklief® (Galderma Laboratories, LP)
Dossier Received: no

Generic Name: Trifarotene

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

Purpose for Class Update:
The acne class has had one new approval, trifarotene cream, and several new product formulations since it was last reviewed in 2018. The purpose of this update is to evaluate new comparative evidence for trifarotene 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 (topical agents of adapalene, adapalene/benzoyl peroxide, tretinoin, tazarotene, benzoyl peroxide, salicylic acid, dapsone, azelaic acid, clindamycin, erythromycin, minocycline, sulfacetamide, trifarotene; oral systemic antibiotics of doxycycline, minocycline, tetracycline, azithromycin, erythromycin, clindamycin, trimethoprim, and sulfamethoxazole/trimethoprim; hormonal agents of oral contraceptives and spironolactone; and oral isotretinoin)?
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:
- There are no new high-quality clinical practice guidelines which have evaluated comparative efficacy and safety of treatments for acne vulgaris.
- 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.
- There are no new randomized trials studying comparative efficacy and harms between treatment regimens for acne vulgaris.
- There is insufficient evidence to determine comparative efficacy and safety of treatments for severe acne.
- 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.

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- 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.

Recommendations:

- Maintain non-preferred designation for trifarotene cream and other new single-source brand formulations on PDL given lack of high-quality data to support use in severe acne.
- No other PDL recommendations based on clinical evidence.
- After evaluation of costs in the executive session, trifarotene (Aklief®) was maintained as non-preferred. Tretinoin (Altreno™) and tazorotene (Arazlo™) will also become non-preferred, while unassigned benzoyl peroxide products will received preferred designation.

Summary of Prior Reviews and Current Policy

- This drug class review is limited by the lack of high-quality evidence from high quality systematic reviews and guidelines which evaluate the comparative efficacy and safety of treatments for severe acne.
- There are also limited randomized controlled trials in the severe acne population and the majority of the trials are older with methodological and conflict of interest concerns.
- There is insufficient evidence to determine comparative efficacy and safety of treatments for severe acne.
- There is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.
- Though not of high methodological quality due to conflict of interest concerns, recent guidelines from the American Academy of Dermatology, European Academy of Dermatology and Venereology, and American Academy of Pediatrics recommend multiple treatment options for severe acne, all including isotretinoin. Other recommended treatments include combination therapy with systemic antibiotics and topical therapies such as benzoyl peroxide, retinoids, or topical antibiotics. Recommendations for treatment of mild to moderate acne generally includes the same therapies, either as monotherapy or in differing combinations, but isotretinoin is generally not recommended until acne is severe.
- Isotretinoin has substantial safety concerns compared to other medications for acne. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin. Because of the teratogenicity risk, it is approved for marketing only under a REMS program called iPLEDGE™.
- Prior authorization (PA) criteria for the Acne preferred drug list (PDL) class, includes federal legend topical medications that have an Food and Drug Administration (FDA) approved and OHA-funded indication for severe acne vulgaris and oral isotretinoin. Use is limited to funded conditions **(Appendix 6)**.
- All single source brand agents are non-preferred and all other agents in the Acne PDL class are preferred.

Background:

Acne vulgaris (AV) is a chronic skin condition that affects approximately 50 million people in the United States.[1] 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.[1] Acne vulgaris is characterized by noninflammatory open or closed comedones and inflammatory lesions.[2] These are generally located on the face, neck, back, chest, and upper arms.[2,3] 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.[1,2]

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.[1,3,4] These are delineated by frequency of papules or pustules and presence and frequency of nodules, as well as presence of hyperpigmentation and erythema.[3] The Physician's Global Assessment (PGA) is a 5-point scale (0-4) that was previously recommended by the FDA to evaluate success in clinical trials of acne vulgaris treatment.[5] 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.[5] More recently, the FDA has given industry guidance to use the Investigator's Global Assessment (IGA) as an ordinal scale to assess overall severity.[6] 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.[6] It should be used in conjunction with separate counting of inflammatory and noninflammatory lesions.[6]

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.[3] Acne fulminans is a severe variant of inflammatory acne that presents with severe ulceration and occasionally the systemic symptoms of fever and arthralgia.[3] 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.[3]

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.[1,2,7] 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.[2,7] Other treatments for severe acne usually include combination therapy with multiple classes of medications which can also be used for mild or moderate acne.[2,7] These classes of medications are well-established and all have been FDA-approved for many years.

Clinically meaningful outcomes for acne assessment include quality of life (QoL) and symptom reduction as demonstrated by decreased lesion counts or lessened acne severity. There are no QoL assessment tools recommended in the FDA guidance to industry[6], 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.[1] 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.[8] 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.[6]

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)**.

Table 1: Acne class prior authorization requests

Time Period	Medication request number	Approval number	Denial number
4th Quarter 2019	99 (1 cancelled)	50 (51%)	48 (48%)
3rd Quarter 2019	39	26 (67%)	12 (31%)
2nd Quarter 2019	71	45 (63%)	26 (37%)
1st Quarter 2019	101 (1 cancelled)	50 (50%)	50 (50%)

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, 2 systematic reviews were excluded due to poor quality[9,10] (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).

Cochrane-Oral isotretinoin for acne
The safety and efficacy of oral isotretinoin for acne vulgaris was assessed in a 2018 Cochrane review.[11] Thirty-one RCTs (n=3836) of patients aged 12-55 years with mild to severe acne were included.[11] Oral isotretinoin was compared to placebo and other therapies for acne vulgaris.[11] These trials were conducted in Asia, Europe, and North America, and outcomes were measured between weeks 8-32 of therapy.[11] All studies but three had a high risk of bias in at least one domain, and 12 of 16 studies were funded by pharmaceutical companies.[11] Additionally, 8 nonrandomized studies were included in the safety data for reporting serious adverse effects.[11]

Three studies (n=400) were included to assess a primary outcome of efficacy of oral isotretinoin versus a combination of oral antibiotics plus topical therapy in patients with moderate to severe acne.[11] Outcomes were assessed at the end of 20 to 24 weeks of treatment.[11] Investigator-assessed inflammatory lesion count was no different between isotretinoin versus comparator groups [Relative risk (RR) 1.01; 95% Confidence interval (95% CI), 0.96 to 1.06; n=400; 3 studies], though isotretinoin may slightly improve acne severity by the physician's global evaluation (RR 1.15; 95% CI, 1.00 to 1.32; n=351; 2 studies).[11] Risk of less serious side effects was higher with isotretinoin (RR 1.67; 95% CI 1.42 to 1.98; n=351; 2 studies). The severe side effect of Stevens-Johnson syndrome was seen once in an isotretinoin patient (RR 3.00; 95% CI, 0.12 to 72.98; n=400; 3 studies).[11] These outcomes were all from low- or very low-quality evidence.[11]

Another primary efficacy outcome involved treatment response based on differing oral isotretinoin doses **(Table 2)**.[11] All outcomes were graded as low-quality evidence.[11] Heterogeneity in the studies precluded a meta-analysis of alternative dose regimens of isotretinoin.[11]

Table 2.[11] Isotretinoin Dose Response

Study/Doses	Result	Time of assessment
Study 1, severe acne (n=154) • 0.05 mg/kg/d • 0.1 mg/kg/d • 0.2 mg/kg/d	Decrease in total inflammatory lesion count • 79% • 80% • 84%	20 weeks
Study 2, severe acne (n=150) • 0.1 mg/kg/d • 0.5 mg/kg/d • 1 mg/kg/d	95% decrease in total inflammatory lesion count • 58% • 80% • 90%	20 weeks
Study 3, moderate acne (n=40) • (A) 0.25-0.4 mg/kg/d continuous low-dose • (B) 0.5-0.7 mg/kg/d continuous conventional dose • (C) 0.5-0.7 mg/kg/d one week each month, intermittent regimen	Decrease in total inflammatory lesion count • [(A) vs. (C)], MD 3.72 lesions; 95% CI, 2.13 to 5.31 • [(B) vs. (C)], MD 3.87 lesions; 95% CI, 2.31 to 5.43	24 weeks

Abbreviations: MD = mean difference; mg/kg/d = milligrams per kilogram per day; 95% CI = 95% confidence interval

No serious adverse events were seen in studies comparing different dosing regimens of isotretinoin (n=906, 14 studies) during treatment duration of 12 to 32 weeks or during follow-up after treatment for up to 48 weeks.[11] Heterogeneity prevented meta-analysis of less serious adverse effects (n=858, 13 studies) such as skin dryness, hair loss, or itching.[11] Safety outcomes were graded as low- to very low-quality evidence.[11]

British Journal of Dermatology-Efficacy and adverse events of oral isotretinoin for acne

The efficacy and safety of oral isotretinoin compared to alternative therapies or placebo in acne vulgaris was assessed in a 2018 British Journal of Dermatology review.[12] Eleven RCTs were included (n=760); only one RCT was assessed as low risk of bias in each of the 9 Cochrane criteria for study quality, while 3 qualified as low risk of bias overall.[12] The age range was 18.0 to 47.9 years, 20.5% of patients were female, and most patients had moderate to severe acne.[12] The trials had placebo control (n=1); active control with oral antibiotics including minocycline, erythromycin, tetracycline, dapsone, doxycycline, or azithromycin (n=7); alternative retinoid etretinate (n=1); and vitamin B complex (n=1).[12] Treatment ranged from 4 weeks to 6 months in duration.[12]

Seven of 11 trials showed statistical significance ($p < 0.05$ for the clinical endpoint of a 10% or greater reduction in acne lesion count) compared to the control group (placebo or active control).[12] All studies with placebo comparison (n=91) and those with alternative controls (etretinate, n=56; vitamin B complex, n=20) found a statistically and clinically significant improvement in patients treated with oral isotretinoin.[12] Results of isotretinoin compared to oral antibiotics (n=593) were more mixed, with only 3 of 7 studies showing statistical significance in favor of isotretinoin treatment.[12] Interpretation is also affected by the variety of antibiotic interventions used between different study protocols.[12]

Adverse reactions were grouped between studies by system given the variation in reporting structure between included trials **(Table 3)**.[12] The authors rated the overall quality of evidence from this review as low.[12]

Table 3. [12] Isotretinoin Adverse Events

Reaction	Adverse event frequency	
	Isotretinoin (n=364)	Control (all active and placebo) (n=384)
Abnormal blood work	15	5
Dermatological reactions	487	227
Ear, nose, and throat	87	35
Gastrointestinal	15	34
Ophthalmological	54	17
Psychiatric	32	19
Other (headache, increased thirst, musculoskeletal pain, tender fingertips, unknown)	61	51
Total	751	388

New Guidelines:

No new clinical practice guidelines were identified.

New Formulations or Indications:

Tretinoin (Altreno™) 0.05% lotion was approved in August 2018 and is indicated for the topical treatment of acne vulgaris in patients 9 years and older.[13] It is a new dosage form of a previously marketed medication.

Minocycline (Amzeeq™) 4% foam was approved in October 2019 to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years and older.[14] Administration via foam vehicle is a novel dosage form for this medication.

Tazarotene (Arazlo™) lotion was approved in January 2020 for the treatment of acne vulgaris in patients 9 years and older.[15] It is a new dosage form of a previously marketed medication.

Dapsone (Aczone®) 7.5% gel indication was expanded to 9 years of age in September of 2019.[16] This labeling change was not applied to the 5% formulation of this medication.

Table 4. Description of Placebo-Controlled Studies of New Formulations

Study	Comparison	Population	Primary Outcome	Results
Gold et al[17] 2 identical studies (04 & 05) MC, DB, VC, RCT, phase 3	FMX101 (4% minocycline foam) vs. Placebo vehicle 2:1 randomization Self-application once daily x 12 weeks in evening Efficacy assessments at weeks 3, 6, 9, 12. Optional open-label continuation x 40 weeks	Age ≥9 years with moderate to severe facial acne. IGA score = 3 to 4; 20 to 50 inflammatory lesions; and 25 to 100 non-inflammatory lesions Study 04 n=466 Study 05 n=495	<u>Coprimary endpoints</u> (1) Absolute change in inflammatory lesion count from baseline to week 12. (2) Rate of IGA-assessed treatment success (score of 0 to 1 plus at least 2-grade improvement)	<u>FMX101 vs vehicle</u> Study 04 (1) -14.13 vs. -11.19; LSM difference 2.8; 95% CI 0.72 to 4.88; p=0.0083 (2) 8.09% vs. 4.77%; RR 1.72; 95% CI 0.73 to 4.05; p=0.2178 Study 05 (1) -13.36 vs. -10.70; LSM difference 3.15; 95% CI 0.95-5.35; p=0.0051 (2) 14.66% vs. 7.89%; RR 1.88, 95% CI 1.02 to 3.46; p=0.0424
Tyring et al[18] 2 identical studies pooled MC, DB, VC, RCT	Tretinoin 0.05% lotion vs. Placebo vehicle 1:1 randomization Self-application once daily x 12 weeks Efficacy assessments at weeks 4, 8, 12.	Age ≥9 years with moderate to severe facial acne. EGSS score of 3 (moderate) or 4 (severe) and lesion counts of 20 to 40 inflammatory lesions and 20 to 100 non-inflammatory lesions n=1640	<u>Coprimary endpoints</u> (1) Absolute change in mean inflammatory lesion count from baseline to week 12 (2) Absolute change in mean non-inflammatory lesion count from baseline to week 12 (3) Proportion of patients with at least 2-grade improvement in EGSS from baseline to week 12	<u>Tretinoin 0.05% lotion vs. vehicle</u> (1) LSM 52.1% vs. 41.0%; 95% CI NR; p<0.001 (2) LSM 46.1% vs. 29.9%; 95% CI NR; p<0.001 (3) NR

Abbreviations: CI = confidence interval, DB = double blind, EGSS = Evaluator Global Severity Score, IGA = Investigator's Global Assessment, LSM = least squares mean, MC = multicenter, NR = not reported; RCT = randomized controlled trial, RR = relative risk, VC = vehicle controlled

New FDA Safety Alerts:

Table 5. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Clindamycin (topical)	Multiple	12/16/2019	Warnings and Precautions	Addition of breastfeeding caution
Dapsone	Aczone	5/18/2018	Adverse Reactions	Identified post-approval reactions for topical product: methemoglobinemia, rash (including erythematous rash, application site rash, and swelling of face (including lip swelling, eye swelling)
Isotretinoin	Absorica, multiple	5/2/2018	Warnings and Precautions	iPLEDGE program: prescriptions must be obtained no later than the "do not dispense to after" date. If not obtained, product must be returned to inventory.
Isotretinoin	Absorica, multiple	11/7/2019	Boxed Warning	Embryo-fetal toxicity and pregnancy contraindication reworded
Mequinol/Tretinoin	Solage	12/2/2019	Warnings and Precautions	Additions of warning of embryo-fetal toxicity, recommendations to use sunscreen and avoid potentially irritating products and weather extremes, and caution of potential to irritate eczematous skin and cause skin fissures added.

Randomized Controlled Trials:

A total of 32 citations were manually reviewed from the initial literature search. After further review, 30 citations were excluded because of wrong study design (eg, observational)[19-36], comparator (eg, no control or placebo-controlled)[37-44], population[45,46], or outcome studied (eg, non-clinical)[47,48]. The remaining 2 trials, which are placebo controlled, include new drug formulations, and are summarized in the table X above. Full abstracts are included in **Appendix 2**.

NEW DRUG EVALUATION:

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: Trifarotene

Trifarotene is a retinoid cream that is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.[49]

Trifarotene is an agonist of the retinoic acid receptors (RAR), with most affinity at the gamma subtype. This contrasts earlier topical retinoids, which target both the beta and gamma subtypes, though the clinical implication of this affinity is unknown.[49,50] Stimulation of RAR is associated with cell differentiation and reduction of inflammation. The exact mechanism for amelioration of acne is unknown.[49]

Trifarotene has been evaluated in two randomized, multicenter, parallel group, double-blind, vehicle-controlled trials with identical design to assess use for the treatment of moderate facial and truncal acne vulgaris [PERFECT 1 (NCT02566369), PERFECT 2 (NCT02556788)].[49,50] Patients aged 9 years and older were treated for up to 12 weeks with trifarotene cream or a placebo vehicle cream.[49,50] Patients were encouraged to moisturize either 1 hour before or after study treatment use.[49,50] Efficacy was assessed with a 5-point IGA for the face and 5-point PGA for the trunk; it is unclear why PGA was chosen for the truncal assessment.[49,50] Moderate acne scores 3 of 5 on these scales.[49,50] Treatment success required IGA/PGA scale achievement of both a minimum 2-point improvement from baseline AND a score of 0 (clear) or 1 (almost clear).[49,50] The IGA is a static evaluation recommended by the FDA for acne severity.[6] The co-primary endpoints related to the face at week 12 and were (1) percentage of subjects achieving IGA scale success as defined above, (2) mean absolute change in facial inflammatory lesion count from baseline, and (3) mean absolute change in facial non-inflammatory lesion count from baseline.[49,50] Co-secondary endpoints were the same indicators described previously but applied to assessment of the trunk and using the PGA scale.[49,50] FDA guidance recommends limiting efficacy assessment to the face, as it is the most frequent site of involvement.[6]

All primary and secondary endpoints were statistically significant but no 95% confidence intervals were provided for any endpoint.[50] **(Table 8**) PERFECT 1 had an overall IGA success of 29.4% for trifarotene, and 19.5% for placebo (ARR 9.9%/NNT 10) and PGA success of 35.7% for trifarotene, and 25.0% for placebo (ARR 10.7%/NNT 9) .[50] Results for PERFECT 2 had higher IGA success rates in both groups, with 42.3% trifarotene and 25.7% placebo (ARR 16.6%/NNT 6) and PGA success of 42.6% trifarotene and 29.9% placebo (ARR 12.7%/NNT 8).[50] Changes in inflammatory lesions, while statistically significant, included high placebo response rates of 35.7 to 51.2% across the various primary and secondary endpoints.[50]
These studies are of low quality, with limitations due to unclear selection bias in both trials and high attrition bias in PERFECT 1. Applicability is limited by low overall response rate in IGA, high placebo response rates in change of lesion count from baseline, and lack of diverse patient group.

Clinical Safety:
Trifarotene cream causes erythema, scaling, dryness, and stinging/burning, reactions tend to be worse early in therapy and lessen over time.[49,50] These adverse reactions were more common in the trifarotene group compared to the placebo group.[49,50] **(Table 6)** Patients will also experience more sensitivity to sun exposure during treatment.[49] Pregnant women were excluded from these phase III studies.[49,50] Fetal adverse effects have been found in animal studies using 800-times the systemic exposure represented in these studies, and oral retinoid use is known to result in birth defects.[49] There are no clinical data for use in lactation.[49] An open-label continuation study of 1 year duration had 2.9% of patients experience an adverse reaction which led to treatment discontinuation.[49]

Table 6: Application Site Tolerability Reactions at Any Post Baseline Visit (p values not reported)[49]

Face	Trifarotene N=1214 Maximum Severity during Treatment (% of patients)			Vehicle cream (placebo) N=1194 Maximum Severity during Treatment (% of patients)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	30.6	28.4	6.2	21	6.8	0.8
Scaling	37.5	27.1	4.9	23.7	5.9	0.3
Dryness	39	29.7	4.8	29.9	6.8	0.8
Stinging/Burning	35.6	20.6	5.9	15.9	3.8	0.5
Trunk	**N=1202**			**N=1185**		
Erythema	26.5	18.9	5.2	12.7	4.4	0.4
Scaling	29.7	13.7	1.7	13.2	2.6	0.1
Dryness	32.9	16.1	1.8	17.8	3.9	0.1
Stinging/Burning	26.1	10.9	4.3	9.2	2.2	0.5

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
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) IGA response
2) Inflammatory lesions
3) Non-inflammatory lesions

Table 7. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Retinoic acid receptor agonist of gamma subtype
Oral Bioavailability	Topical (n/a)
Distribution and Protein Binding	99.9% plasma protein bound
Elimination	Primarily feces
Half-Life	2-9 hours
Metabolism	CYP2C9, CYP3A4, CYP3C8, CYP2B6 (minor)

Table 8. 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. Tan et al[49,50] Phase 3, DB, DB, RCT PERFECT 1 NCT02566369	1. Trifarotene cream 50 mcg/g once daily at bedtime x 12 weeks (T) 2. Placebo vehicle cream once daily at bedtime x 12 weeks (P) Both groups instructed to cleanse skin before application. Moisturizer use was encouraged, but to be avoided 1 hr before or after study drug application. Dosing could be changed by investigator to every other day x 2 weeks, within first 4 weeks from baseline assessment if needed to manage irritation.	Demographics: Age (mean, SD): 19.4 ± 6.41 Male: 579 (47.9%) White: 992 (82.1%) Skin phototype Type I: 65 (5.4%) Type II: 379 (31.4%) Type III: 460 (38.1%) Type IV: 188 (15.6%) Type V: 91 (7.5%) Type VI: 25 (2.1%) Baseline lesions (Face) (mean ± SD) Inflammatory: 34.8 ± 13.31 Noninflammatory: 53.4 ±27.35 Baseline lesions (Trunk) Inflammatory: 35.3 ±17.32 Noninflammatory: 46.9 ± 21.75 Key Inclusion Criteria: -age ≥9 years -moderate facial acne (IGA score 3, ≥20 inflammatory lesions, and ≥25 noninflammatory lesions) AND moderate truncal acne* (PGA score of 3, ≥20 inflammatory lesions, and 20-99 noninflammatory lesions on trunk and	ITT: 1. 612 2. 596 Attrition: 1. 72 (11.8%) 2. 61 (10.2%)	Primary Endpt (FACE) # (%): *IGA success* (2 point improvement AND overall score of clear to almost clear) T:180 (29.4) P: 116 (19.5) p<0.001 (95% CI NR) *Inflammatory lesions:* Mean absolute Δ from baseline T: -19 (-54.4) P: -15.4 (-44.8) p<0.001 (95% CI NR) *Noninflammatory lesions:* Mean absolute Δ from baseline T: -25 (-49.7) P: -17.9 (-35.7) p<0.001 (95% CI NR) Secondary Endpt (TRUNK) # (%): *PGA success* (2 point improvement AND overall score of clear to almost clear) T: 214 (35.7) P: 146 (25.0) p<0.001 (95% CI NR) *Inflammatory lesions:* Mean absolute Δ from baseline T: -21.4 (-57.4) P: -18.8 (-50.0) p<0.001 (95% CI NR) *Noninflammatory lesions:* Mean absolute Δ from baseline T: -21.9 (-49.1) P: -17.8 (-40.3)	9.9%/ 10 10.7% /9	Severe AE (# of patients): T: 6 P: 0 Study w/d due to AE (%): T: 1.9% P: 0%	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomization stratified by study center but described as both "interactive response technology" and "randomization list generated by statistician and provided to packaging organization for labeling" Performance Bias: (low) Topical medication in identical packaging, subjects instructed not to discuss appearance of drug with investigators/evaluators; randomization list locked to non-designated personnel. Detection Bias: (low) Assessors all trained in study-specific measurements and were blinded. Patients were primarily assessed by same evaluator during study for continuity. Attrition Bias: (high) Discontinuation rate of 11% in short term study. Discontinuations due to "withdrawal by subject" not itemized by reason. Adverse events causing withdrawal were much more frequent in intervention group. ITT analysis with multiple imputation methodology used for missing values. Reporting Bias: (low) All prespecified outcome presented, however, p-values reported without CI. Other Bias: (high) industry funded **Applicability**: Patient: Patients predominantly white and with skin phototype I or II (of VI), limiting applicability to other skin types (e.g. African-Americans or Latinos). Intervention: Intervention appropriate with use of FDA approved product and allowance for home moisturizer use. Comparator: Placebo appropriate, but comparison with active comparator would enable comparative assessment of clinical efficacy. Outcomes: IGA/PGA and lesion count are common outcomes in acne assessment.

		reachable for self-application) *criterion waived for 9-11 year olds due to rarity in this age group <u>Exclusion Criteria</u>: -severe acne - >1 nodule on face - >1 nodule on trunk -presence of acne cysts, beard, facial hair, or tattoos that could interfere with assessments -uncontrolled or serious medical condition -significantly abnormal lab values -drug sensitivities -pregnancy, lactation, or intent to conceive		p<0.001 (95% CI NR)				<u>Setting</u>: Over 100 study sites across the United States, Canada, Russia, and Europe; all countries with a predominantly white population.
2. Tan et al[49,50] Phase 3, DB, DB, RCT PERFECT 2 NCT02556788	Identical to PERFECT 1 above 1. Trifarotene cream 50 mcg/g once daily at bedtime x 12 weeks (T) 2. Placebo vehicle cream once daily at bedtime x 12 weeks (P) Both groups instructed to cleanse skin before application. Moisturizer use was encouraged, but to be avoided 1 hr before or	<u>Demographics</u>: Age (mean, SD): 19.7 ± 6.3 Male: 517 (42.7%) White: 1119 (92.3%) Skin phototype Type I: 73 (6%) Type II: 523 (43.2%) Type III: 481(39.7%) Type IV: 71 (5.9%) Type V: 33 (2.7%) Type VI: 31 (2.6%) Baseline lesions (Face) (mean ± SD) Inflammatory: 36.6 ± 13.84 Noninflammatory: 50.9 ±25.83 Baseline lesions (Trunk)	<u>ITT</u>: 1. 602 2. 610 <u>Attrition</u>: 1. 44 (7.3%) 2. 37 (6.1%)	<u>Primary Endpt (FACE)</u> # (%): *IGA success* Trifarotene 255 (42.3) Placebo 157 (25.7) p<0.001 (95% CI NR) *Inflammatory lesions:* Mean absolute Δ from baseline Trifarotene -24.2 (-66.2) Placebo -18.7 (-51.2) p<0.001 (95% CI NR) *Noninflammatory lesions:* Mean absolute Δ from baseline Trifarotene -30.1 (-57.7) Placebo -21.6 (-43.9) p<0.001 (95% CI NR) <u>Secondary Endpt (TRUNK)</u> # (%): *PGA success* Trifarotene 255 (42.6) Placebo 182 (29.9)	16.6% /6 12.7% /8	<u>Severe AE (# of patients):</u> T: 3 P: 0 <u>Study w/d due to AE (# of patients):</u> T: 1.2% P: 0%		**Risk of Bias (low/high/unclear)**: See PERFECT 1 **Applicability**: <u>Patient</u>: Patients predominantly white and with skin phototype I or II (of VI), limiting applicability to other skin types (e.g. African-Americans or Latinos). <u>Intervention</u>: Intervention appropriate <u>Comparator</u>: Placebo appropriate, but comparison with active comparator would enable comparative assessment of clinical efficacy. <u>Outcomes</u>: IGA/PGA and lesion count are common outcomes in acne assessment. <u>Setting</u>: Over 100 study sites across the United States, Canada, Russia, and Europe; all countries with a predominantly white population.

	after study drug application. Dosing could be changed by investigator to every other day x 2 weeks, within first 4 weeks from baseline assessment if needed to manage irritation.	Inflammatory: 39.1 ±16.82 Noninflammatory: 45.9 ± 19.87 <u>Key Inclusion Criteria</u>: -identical to PERFECT 1 <u>Key Exclusion Criteria</u>: -identical to PERFECT 1		p<0.001 (95% CI NR) *Inflammatory lesions:* Mean absolute Δ from baseline Trifarotene -25.5 (-65.4%) Placebo –19.8 (51.1) p<0.001 (95% CI NR) *Noninflammatory lesions:* Mean absolute Δ from baseline Trifarotene -25.9 (-55.2) Placebo –20.8 (45.1%) p<0.001 (95% CI NR)				
<u>Abbreviations</u>: AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; IGA = Investigator's Global Assessment; ITT = intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PGA = Physician's Global Assessment; P = placebo vehicle cream group; PP = per protocol; SD = standard deviation; T = trifarotene group; w/d = withdrawal								

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Appendix 1: Current Preferred Drug List

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

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

benzoyl peroxide	PANOXYL	CLEANSER	TP	N
benzoyl peroxide	PANOXYL-4	CLEANSER	TP	N
benzoyl peroxide	BPO	GEL (GRAM)	TP	N
clindamycin phos/benzoyl perox	ONEXTON	GEL (GRAM)	TP	N
clindamycin phos/benzoyl perox	ONEXTON	GEL W/PUMP	TP	N
clindamycin phos/skin clnsr 19	CLINDACIN ETZ	KIT	TP	N
clindamycin phos/skin clnsr 19	CLINDACIN PAC	KIT	TP	N
clindamycin phosphate	CLINDAGEL	GEL DAILY	TP	N
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	GEL DAILY	TP	N
clindamycin/benzoyl/emol cmb94	NEUAC	CMB CR GEL	TP	N
dapsone	ACZONE	GEL W/PUMP	TP	N
erythromycin/benzoyl peroxide	BENZAMYCIN	GEL (GRAM)	TP	N
erythromycin/benzoyl peroxide	ERYTHROMYCIN-BENZOYL PEROXIDE	GEL (GRAM)	TP	N
isotretinoin	ABSORICA	CAPSULE	PO	N
tazarotene	FABIOR	FOAM	TP	N
tretinoin	TRETIN-X	CREAM (G)	TP	N
tretinoin microspheres	RETIN-A MICRO PUMP	GEL W/PUMP	TP	N
tretinoin/emol 9/skin cleansr1	TRETIN-X	COMBO. PKG	TP	N
trifarotene	AKLIEF	CREAM (G)	TP	N
benzoyl peroxide	BENZOYL PEROXIDE	CLEANSER	TP	
benzoyl peroxide	PANOXYL	CLEANSER	TP	
benzoyl peroxide	CLEARASIL DAILY CLEAR	CREAM (G)	TP	
benzoyl peroxide	DEL-AQUA-10	CREAM (G)	TP	
benzoyl peroxide	ACNE MEDICATION	LOTION	TP	
benzoyl peroxide	BENZOYL PEROXIDE	LOTION	TP	
tretinoin	ALTRENO	LOTION	TP	

Appendix 2: Abstracts of Comparative Clinical Trials

A novel topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: Results of 2 randomized, double-blind, phase 3 studies
Gold LS, Dhawan S, Weiss J, Draelos ZD, Ellman H, Stuart IA

Background
FMX101 4% is a topical minocycline foam for the treatment of moderate-to-severe acne.
Objective
Evaluate the efficacy and safety of FMX101 4% in treating moderate-to-severe acne vulgaris.
Methods
Two identical phase 3 studies were conducted. Subjects were randomized 2:1 to once-daily FMX101 4% or foam vehicle for 12 weeks. The coprimary end points were the change in inflammatory lesion count from baseline and the rate of treatment success according to the Investigator's Global Assessment (a score of 0 or 1 for clear or almost clear, with a ≥2-grade improvement) at week 12.
Results
A total of 961 subjects were enrolled (study 04, N = 466; study 05, N = 495). Compared with vehicle, FMX101 4% demonstrated a significantly greater reduction in inflammatory lesions in both studies ($P < .05$) and a greater rate of treatment success in study 05 according to the Investigator's Global Assessment ($P < .05$). Pooled analyses of the 2 studies demonstrated statistical significance for both coprimary end points (all $P < .05$). Noninflammatory lesion count was also significantly reduced with FMX101 4% versus with vehicle in both studies. FMX101 4% was generally safe and well tolerated. Skin-related adverse events were reported in less than 1% of subjects treated with FMX101 4%.
Limitations
Longer-term efficacy and safety outcomes are needed (ongoing).
Conclusion
FMX101 4% topical minocycline foam significantly reduced both inflammatory and noninflammatory lesions and improved Investigator's Global Assessment scores in patients with moderate-to-severe acne.
J Am Acad Dermatol 2019;80:168-77
https://doi.org/10.1016/j.jaad.2018.08.020

Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Assessment of Efficacy and Safety in Patients Aged 9 Years and Older
Tyring SK, Kircik LH, Pariser DM, Guenin E, Bhatt V, Pillai R

Background
Topical tretinoin has been extensively studied in clinical trials, and its essential role in the treatment of acne vulgaris (acne) established through evidence-based guidelines.
Objective
To evaluate efficacy, safety, and tolerability of a novel tretinoin 0.05% lotion in moderate-to-severe acne in patients aged 9 years and older. Methods: A total of 1640 patients, 9-58 years of age were randomized to receive tretinoin 0.05% lotion or vehicle in two double-blind, placebo-controlled 12-week, 2-arm, parallel group studies evaluating safety and efficacy (inflammatory and noninflammatory lesion counts and acne severity using Evaluator Global Severity Scores [EGSS]).

In addition, patients completed a patient satisfaction survey (PSS), Acne-specific quality of life (QoL) questionnaire and assessed their facial skin for shininess/oiliness improvement. The data from these two independent studies were pooled and analyzed.

Results

Tretinoin 0.05% lotion demonstrated statistically significant superiority to vehicle in reducing inflammatory and noninflammatory lesion counts (both P less than .001) at week 12 and improving acne severity (P less than .001). At week 12, mean percent change in inflammatory and noninflammatory lesions were 52% and 46%, respectively. Treatment success (a 2-grade improvement in EGSS and 'clear' or 'almost clear' was reported in 18% of patients. Tretinoin 0.05% lotion also showed significantly greater benefits relative to vehicle control in terms of patient satisfaction (P less than .001) and acne-specific QoL domains. Tretinoin 0.05% lotion was very well tolerated with no substantive differences in cutaneous tolerability among treatment groups. No patients discontinued treatment because of adverse events.

Limitations

Data from controlled studies may differ from clinical practice.

Conclusions:

Tretinoin 0.05% lotion provides statistically significant greater efficacy than vehicle with a highly favorable safety and tolerability profile in moderate-to-severe acne patients.

J Drugs Dermatol. 2018;17(10):1084-1091.

Appendix 3: Medline Search Strategy

Step	Search Term	Article #
1	Adapalene/tu, to [Therapeutic Use, Toxicity]	20
2	azelaic acid.mp.	721
3	Benzoyl Peroxide/tu, to [Therapeutic Use, Toxicity]	511
4	Clindamycin/tu, to [Therapeutic Use, Toxicity]	2840
5	Dapsone/tu, th, to [Therapeutic Use, Therapy, Toxicity]	2890
6	Erythromycin/tu, th, to [Therapeutic Use, Therapy, Toxicity]	4499
7	Isotretinoin/tu, to [Therapeutic Use, Toxicity]	1438
8	Sulfacetamide/tu, th, to [Therapeutic Use, Therapy, Toxicity]	109
9	Tretinoin/tu, to [Therapeutic Use, Toxicity]	4089
10	tazarotene.mp.	565
11	trifarotene.mp.	10
12	Contraceptives, Oral/tu, th, to [Therapeutic Use, Therapy, Toxicity]	1542
13	Acne Vulgaris/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]	6727
14	Acne Conglobata/dt, th [Drug Therapy, Therapy]	5
15	acne fulminans.mp.	178
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	18477
17	13 or 14 or 15	6816
18	16 and 17	1792
19	limit 18 to (english language and yr="2018 -Current" and (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 pragmatic clinical trial or randomized controlled trial or "systematic review"))	28 *24 after duplicates removed

Additional articles found via hand searching of reviews.

Appendix 4: Prescribing Information Highlights

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

AKLIEF® (trifarotene) cream, for topical use
Initial U.S. Approval: 2019

---------- INDICATIONS AND USAGE ----------
AKLIEF Cream is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- For topical use only. Not for oral, ophthalmic or intravaginal use.
- Apply a thin layer of AKLIEF Cream to the affected areas of the face and/or trunk once a day, in the evening, on clean and dry skin. Avoid contact with the eyes, lips, paranasal creases, and mucous membranes. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Cream: 0.005% trifarotene. (3)

---------- CONTRAINDICATIONS ----------
None (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Skin irritation: Erythema, scaling, dryness, and stinging/burning may be experienced with use of AKLIEF Cream. Use a moisturizer from the initiation of treatment, and, if appropriate, reduce the frequency of application of AKLIEF Cream, suspend or discontinue use. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided. (5.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥ 1%) in patients treated with AKLIEF Cream were application site irritation, application site pruritus, and sunburn (6).

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

Revised: 10/2019

Appendix 5: Key Inclusion Criteria

Population	Adults and children with acne conglablata, acne fulminans, or severe acne vulgaris
Intervention	Trifarotene topical therapy, other acne therapies (see appendix 3)
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.