PDL DRUG REVIEW

Proprietary Name: Aklief®
Common Name: trifarotene
PDL Category: Topical-Acne Preparations

Comparable Products	Preferred Drug List Status
Adapalene	Preferred with Conditions
Retin-A	Preferred with Conditions
Tazorac	Preferred with Conditions

Summary

Pharmacology/Usage: Trifarotene, the active ingredient of Aklief®, is a terphenyl acid derivative and is a retinoid. It is an agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR. Stimulation of RAR results in modulation of target genes, which are associated with various processes, including cell differentiation and mediation of inflammation. The exact mechanism of action by which trifarotene works for acne is not known.

Indication: For the topical treatment of acne vulgaris in patients 9 years of age and older.

There is no pregnancy category for this medication; however, the risk summary indicates that available data from clinical trials with use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are case reports of major birth defects similar to those seen in fetuses exposed to oral retinoids in pregnant women exposed to other topical retinoids, but these case reports do not establish a pattern or association with retinoid-related embryopathy. The safety and efficacy of use in the pediatric population under the age of 9 years have not been established.

Dosage Form: Cream, 0.005%. Each gram contains 50mcg of trifarotene

Recommended Dosage: Apply a thin layer to the affected areas once daily, in the evening, on clean and dry skin.

- One pump actuation should be sufficient to cover the face (i.e. forehead, cheeks, nose, and chin).
- Two actuations of the pump should be sufficient to cover the upper trunk (i.e. reachable upper back, shoulders, and chest). One additional pump actuation may be used for middle and lower back if acne is present

The use of a moisturizer is recommended as frequently as needed from the start of treatment. Avoid contact with the eyes, lips, paranasal creases, and mucus membranes.

Drug Interactions: Topical application of Aklief® Cream is not expected to affect the circulating concentrations of oral hormonal contraceptives containing ethinyl estradiol and levonorgestrel.

Box Warnings: There are no box warnings listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Aklief® cream) minus reported % incidence for vehicle cream. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included application site irritation (7.2%), application site pruritus (1.6%), and sunburn (2.1%).

Additional adverse reactions that were reported at a frequency of <1% in subjects treated with Aklief® included application site pain, application site dryness, application site discoloration, application site rash, application site swelling, application site erosion, acne, dermatitis allergic, and erythema.

Application site tolerability reactions were assessed for both the face and the trunk.

Listed % incidence for adverse drug reactions= reported % incidence for drug (Aklief® cream) minus reported % incidence for vehicle cream of mild/moderate/severe severity on the face. The most frequently reported adverse events included erythema (9.6%/21.6%/5.4%), scaling (13.8%/21.2%/4.6%), dryness (9.1%/22.9%/4%), and stinging/burning (19.7%/16.8%/5.4%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Aklief® cream) minus reported % incidence for vehicle cream of mild/moderate/severe severity on the trunk. The most frequently reported adverse events included erythema (13.8%/14.5%/4.8%), scaling (16.5%/11.1%/1.6%), dryness (15.1%/12.2%/1.7%), and stinging/burning (16.9%/8.7%/3.8%).

Avoid application of Aklief® to cuts, abrasions, or eczematous or sunburned skin. Use of 'waxing' as a depilatory method should be avoided on skin treated with Aklief® cream.

Minimize unprotected exposure to ultraviolet rays, including sunlight and sunlamps, during treatment with Aklief®. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to use caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Galderma Labs

Analysis: The safety and efficacy of use of Aklief® cream in the treatment of moderate facial and truncal acne vulgaris were assessed in 2 randomized, multicenter, parallel group, double-blind, vehicle-controlled trials of identical design. The trials included subjects 9 years of age and older (N=2420) who were treated for up to 12 weeks with either Aklief® cream or vehicle cream. Subjects were encouraged to use a moisturizer as desired, while allowing about a 1-hour period before or after the study treatment application.

Overall, 87% of subjects included in the trials were Caucasian and 55% were female. Regarding age, 1.4% of subjects were 9 to 11 years of age, 47% were 12 to 17 years of age, and 52% were 18 years of age and older. All subjects had moderate acne vulgaris and 99% of subjects had moderate acne vulgaris on the trunk. At baseline, subjects had between 7 and 200 (average 36) inflammatory lesions on the face and between 0 and 220 (average 38) on the trunk. In addition, subjects had 21 to 305 (average 52) non-inflammatory lesions on the face and 0 to 260 (average 46) on the trunk.

Acne severity was assessed using a 5-point Investigator's Global Assessment (IGA) scale for the face and a 5-point Physician's Global Assessment (PGA) scale for the trunk, with moderate acne vulgaris defined as a score of 3. Success on the IGA/PGA scale was defined as achieving a score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline. The co-primary endpoints (evaluated on the face) were the % of subjects achieving success on the IGA scale, the mean absolute change in facial inflammatory lesion count from baseline, and the mean absolute change in facial non-inflammatory lesion count from baseline, all assessed at week 12. The co-secondary endpoints (assessed on the trunk) were the % of subjects achieving success on the PGA scale, the mean absolute change in truncal inflammatory lesion count from baseline, and the mean absolute change in truncal non-inflammatory lesion count from baseline, all assessed at week 12. Efficacy results can be seen in the tables below, which were adapted from the prescribing information.

This table includes acne of the face efficacy results at week 12.

	Study 1		Study 2	
	Aklief® Cream	Vehicle Cream	Aklief® Cream	Vehicle Cream
	N=612	N=596	N=602	N=610
IGA Success: At least a 2-grade improvement & clear (0) or almost clear (1)	29.4%	19.5%	42.3%	25.7%
Inflammatory Lesions: mean, absolute (%) change from baseline	-19 (-54.4%)	-15.4 (-44.8%)	-24.2 (-66.2%)	-18.7 (-51.2%)
Non-Inflammatory Lesions: mean, absolute (%) change from baseline	-25 (-49.7%)	-17.9 (-35.7%)	-30.1% (-57.7%)	-21.6 (-43.9%)

This table includes acne of the trunk efficacy results at week 12.

	Study 1		Study 2	
	Aklief® Cream	Vehicle Cream	Aklief® Cream	Vehicle Cream
	N=600	N=585	N=598	N=609
PGA Success: At least a 2-grade improvement & clear (0) or almost clear (1)	35.7%	25%	42.6%	29.9%
Inflammatory Lesions: mean, absolute (%) change from baseline	-21.4 (-57.4%)	-18.8 (-50.0%)	-25.5 (-65.4%)	-19.8 (-51.1%)
Non-Inflammatory Lesions: mean, absolute (%) change from baseline	-21.9 (-49.1%)	-17.8 (-40.3%)	-25.9% (-55.2%)	-20.8 (-45.1%)

Place in Therapy: Aklief® cream is a topical retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. Trifarotene is the first in its class of RAR-gamma selective topical retinoid. In 2 randomized, vehicle-controlled trials, Aklief® cream was found to be more effective than vehicle for its primary endpoints. Per the full-text study by Tan et al[2], the facial and truncal success rates per the IGA and PGA, respectively, as well as the changes in inflammatory and non-inflammatory lesion counts were all significantly ($p<0.001$) in favor of trifarotene when compared with vehicle. In a long-term 52-week study by Blune-Peytavi et al[3], trifarotene was found to be safe, well-tolerated, and effective in moderate facial and truncal acne.

There is no evidence at this time that Aklief® cream is safer or more effective than the currently preferred medications. It is therefore recommended that Aklief® cream remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Aklief [package insert]. Fort Worth, Texas: Galderma Laboratories; 2019.
[2] Tan J, Thiboutot D, Popp G, et al. Randomized phase 3 evaluation of trifarotene 50mcg/g cream treatment of moderate facial and truncal acne. *J Am Acad Dermatol.* 2019; 80(6): 1691-1699.
[3] Blume-Peytavi U, Fowler J, Lemeny L, et al. Long-term safety and efficacy of trifarotene 50mcg/g cream, a first-in-class RAR-γ selective topical retinoid, in patients with moderate facial and truncal acne. J Eur Acad Dermatol Venereol. 2019. [Epub ahead of print].