

## 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  $\geq$  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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 10/2023

## FULL PRESCRIBING INFORMATION: CONTENTS\*

<b>1 INDICATIONS AND USAGE</b>	8.5 Geriatric Use
<b>2 DOSAGE AND ADMINISTRATION</b>	<b>11 DESCRIPTION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>	<b>12 CLINICAL PHARMACOLOGY</b>
<b>4 CONTRAINDICATIONS</b>	12.1 Mechanism of Action
<b>5 WARNINGS AND PRECAUTIONS</b>	12.2 Pharmacodynamics
5.1 Skin Irritation	12.3 Pharmacokinetics
5.2 Ultraviolet Light and Environmental Exposure	<b>13 NONCLINICAL TOXICOLOGY</b>
<b>6 ADVERSE REACTIONS</b>	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
6.1 Clinical Trials Experience	<b>14 CLINICAL STUDIES</b>
<b>7 DRUG INTERACTIONS</b>	<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>	<b>17 PATIENT COUNSELING INFORMATION</b>
8.1 Pregnancy	*Sections or subsections omitted from the full prescribing information are not listed.
8.2 Lactation	
8.4 Pediatric Use	

## FULL PRESCRIBING INFORMATION

- 1 INDICATIONS AND USAGE**  
AKLIEF Cream is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.
- 2 DOSAGE AND ADMINISTRATION**  
Apply a thin layer of AKLIEF Cream to the affected areas once daily, in the evening, on clean and dry skin.
- One pump actuation should be enough to cover the face (i.e., forehead, cheeks, nose, and chin).
  - Two actuations of the pump should be enough 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 initiation of treatment.
- Avoid contact with the eyes, lips, paranasal creases, mucous membranes. AKLIEF Cream is for topical use only. Not for oral, ophthalmic, or intravaginal use.
- 3 DOSAGE FORMS AND STRENGTHS**  
Cream: 0.005%. Each gram of AKLIEF Cream contains 50 mcg of trifarotene in a white cream.
- 4 CONTRAINDICATIONS**  
None
- 5 WARNINGS AND PRECAUTIONS**
- 5.1 Skin Irritation**  
Patients using AKLIEF Cream may experience erythema, scaling, dryness, and stinging/burning. Maximum severity of these reactions typically occurred within the first 4 weeks of treatment, and severity decreased with continued use of the medication. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of application of AKLIEF Cream, or suspend use temporarily. If severe reactions persist the treatment may be discontinued. 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.
- 5.2 Ultraviolet Light and Environmental Exposure**  
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 exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.
- 6 ADVERSE REACTIONS**
- 6.1 Clinical trials experience**  
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect rates observed in practice. In the three Phase 3 clinical trials, a total of 1673 subjects with acne vulgaris on the face and trunk, 9 years and older were exposed to AKLIEF Cream. Of these, 1220 subjects were treated once daily for up to 12 weeks and 453 were treated once daily for up to 1 year. Adverse reactions reported in the 2 randomized, double-blind, vehicle-controlled 12-week clinical trials in  $\geq$ 1.0% of subjects treated with AKLIEF Cream (and for which the rate exceeded the rate for vehicle), as well as the corresponding rates reported in subjects treated with the vehicle cream are presented in Table 1.

**Table 1. Adverse Reactions Occurring in  $\geq$  1.0% of Subjects with Acne Vulgaris of the Face and Trunk in the Two 12-week Phase 3 Clinical Trials**

Preferred Term	AKLIEF Cream (N= 1220)	Vehicle Cream (N=1200)
Application site irritation	91 (7.5)	4 (0.3)
Application site pruritus	29 (2.4)	10 (0.8)
Sunburn	32 (2.6)	6 (0.5)

Additional adverse reactions that were reported in more than one subject treated with AKLIEF Cream (and at a frequency <1%) included application site pain, application site dryness, application site discoloration, application site rash, application site swelling, application site erosion, acne, dermatitis allergic, and erythema.

In the one-year, open-label safety trial that included 453 subjects 9 years and older, with acne vulgaris of the face and trunk, the pattern of adverse reactions for AKLIEF Cream was similar to that experienced in the 12-week controlled trials. A total of 12.6% of subjects had at least one adverse reaction during the trial, and 2.9% of subjects had an adverse reaction leading to treatment discontinuation. The most common adverse reactions ( $\geq$  1% of subjects) for the entire trial were application site pruritus (4.6%), application site irritation (4.2%), and sunburn (5.5%). The frequency of adverse reactions decreased over time.

Skin irritation was evaluated by active assessment of erythema, scaling, dryness, and stinging/burning and collected separately. In the two 12-week Phase 3 clinical trials, these signs/symptoms were assessed at baseline and at least one post-baseline visit, in 1214 subjects (for face) and 1202 subjects (for trunk) treated with AKLIEF Cream. The percentage of subjects who were assessed to have these signs and symptoms at any post baseline visit and at a severity worse than baseline are summarized in Table 2.

**Table 2. Application Site Tolerability Reactions at Any Post Baseline Visit**

Face	AKLIEF Cream N=1214 Maximum Severity during Treatment			Vehicle Cream N=1194 Maximum Severity during Treatment		
	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%

Local tolerability on the face in subjects treated with AKLIEF Cream worsened for any of the signs/symptoms compared with baseline to a score of moderate for up to 30% of subjects, or severe for up to 6% of subjects. On the trunk, the corresponding percentages were up to 19% (moderate) and up to 5% (severe). The scores reached maximum severity at Week 1 for the face, and at Week 2 to 4 of treatment for the trunk, and decreased thereafter.

In the open-label, 1-year Phase 3 trial, the local tolerability profile was comparable to that observed in the two pivotal Phase 3 trials.

## 7 DRUG INTERACTIONS

Topical application of AKLIEF Cream is not expected to affect the circulating concentrations of oral hormonal contraceptives containing ethinyl estradiol and levonorgestrel.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available data from clinical trials with AKLIEF Cream 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.

In animal reproduction studies, oral doses of trifarotene administered to pregnant rats and rabbits during organogenesis that resulted in systemic exposures more than 800 times the systemic exposure at the maximum recommended human dose (MRHD) of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths and external, visceral, and skeletal malformations (*see Data*). The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Data

##### Animal Data

Oral administration of trifarotene to pregnant rats during the period of organogenesis at doses that resulted in systemic exposures greater than 1600 times those in humans at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths, reduced mean fetal weight, and external, visceral, and skeletal malformations. Oral administration of trifarotene to pregnant rabbits during the period of organogenesis at doses that resulted in systemic exposures at least 800 times those in humans at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including defects of the tail, limbs, urogenital organs, and vertebral column.

Trifarotene administered orally to female rats from gestation Day 6 to lactation Day 20, at doses that resulted in systemic exposures up to 594 times those in humans at the MRHD of AKLIEF Cream, had no effect on maternal function or behavior, including gestation, delivery, pup-rearing, lactation and nursing, or survival or development of pups. There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

### 8.2 Lactation

#### Risk Summary

There are no data on the presence of trifarotene in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, trifarotene was present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topical administration of large amounts of trifarotene could result in sufficient systemic absorption to produce detectable quantities in human milk (*see Clinical Considerations*). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AKLIEF Cream and any potential adverse effects on the breastfed infant from AKLIEF Cream or from the underlying maternal condition.

#### Clinical Considerations

To minimize potential exposure to the breastfed infant via breastmilk, use AKLIEF Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply AKLIEF Cream directly to the nipple and areola to avoid direct infant exposure.

### 8.4 Pediatric Use

Safety and effectiveness of AKLIEF Cream for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years to 17 years based on evidence from well-controlled clinical trials, long-term safety trial, and a pharmacokinetic trial.

## Patient Information AKLIEF® (trifarotene) cream

**Important:** AKLIEF Cream is for use on the skin only. Do not use AKLIEF Cream in your mouth, eyes, or vagina.

### What is AKLIEF Cream?

AKLIEF Cream is a prescription medicine used on the skin (topical) to treat acne vulgaris in people 9 years of age and older. It is not known if AKLIEF Cream is safe and effective in children younger than 9 years old.

**Before using AKLIEF Cream, tell your healthcare provider about all of your medical conditions, including if you:**

- have skin problems, including eczema, cuts or sunburn
- are pregnant or planning to become pregnant. It is not known if AKLIEF Cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AKLIEF Cream passes into your breast milk. Breastfeeding women should use AKLIEF Cream on the smallest area of skin and for the shortest time needed while breastfeeding. Do not apply AKLIEF Cream to the nipple and areola to avoid contact with your baby.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins and herbal supplements.

Especially tell your healthcare provider if you use any other medicine for acne.

### How should I use AKLIEF Cream?

- Use AKLIEF Cream exactly as your healthcare provider tells you to use it. Apply a thin layer of AKLIEF Cream over the affected areas 1 time each day, in the evening.

### Applying AKLIEF Cream:

- Wash the area where the cream will be applied and pat dry.
- If you receive a sample tube of AKLIEF Cream, follow your healthcare provider’s instructions about how much to apply.
- AKLIEF Cream comes in a pump.
  - Press down on (depress) the pump 1 time to dispense a small amount of AKLIEF Cream and spread a thin layer over your face (forehead, cheeks, nose, and chin). Avoid contact with your eyes, lips, mouth, and the corners of your nose.
  - Press down on the pump 2 times to dispense enough AKLIEF Cream to apply a thin layer to cover your upper trunk (the area of your upper back that you can reach, shoulders, and chest). One more pump may be used to apply a thin layer of AKLIEF Cream to your middle and lower back, if acne is present.

