# TRIFAROTENE

## AKLIEF®

50 mcg/g cream
Anti-Acne

**PRODUCT DESCRIPTION**
White and homogeneous preparation

**FORMULATION**
Each gram contains:
Trifarotene .....50 mcg

**PHARMACODYNAMICS AND PHARMACOKINETICS**

**Pharmacodynamics**
At the approved recommended dosage, Trifarotene (Aklief) Cream does not prolong the QT interval to any clinically relevant extent.

**Pharmacokinetics**
Pharmacokinetics of trifarotene was evaluated in a study involving 19 adult subjects with acne vulgaris following once daily application of Trifarotene (Aklief) Cream for 29 days (daily dose range 1.5 g/day to 2 g/day) to the face, shoulders, chest and upper back.

Absorption
Systemic concentrations were at steady state following 2 weeks of treatment and were quantifiable in 7 subjects. Steady state Cmax ranged from below the limit of quantification (less than 5 pg/mL) to 10 pg/mL and AUC0-24h ranged from 75 to 104 pg.h/mL in adults. No drug accumulation is expected with long-term use.
Distribution Plasma protein binding is approximately 99.9%.

Elimination
The terminal half-life ranged from 2 to 9 hours.

Metabolism
Trifarotene is primarily metabolized by CYP2C9, CYP3A4, CYP2C8, and to a lesser extent by CYP2B6 in vitro.

Excretion
Trifarotene is primarily excreted by the feces.

Specific Populations
*Pediatric Patients*
Steady state Cmax ranged from less than 5 pg/mL to 9 pg/mL and AUC0-24h ranged from 89 to 106 pg.h/mL in pediatrics (10 to 17- years-old). Steady state conditions were achieved in patients following 2 weeks of topical administration. No drug accumulation is expected with long-term use.

Drug Interactions Studies
*Clinical Studies and Model-Based Approaches*
No clinically significant differences in the pharmacokinetics of trifarotene were predicted when used concomitantly with fluconazole (a moderate CYP2C9 and CYP3A inhibitor).
*In Vitro Studies*
Cytochrome P450 (CYP) Enzymes: AKLIEF Cream is not expected to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, or induce CYP1A2, 2B6, and 3A4.
*Transporter Systems:* Trifarotene (Aklief) Cream is not expected to inhibit MATE, OATP, OAT, OCT, BCRP, Pgp,BSEP, or MRP.

**INDICATIONS**
Trifarotene (Aklief) Cream is a retinoid indicated for the topical treatment of Acne Vulgaris in patients 9 years of age and older.
Trifarotene (Aklief) is indicated for the cutaneous treatment of Acne Vulgaris of the face and/or the trunk in patients from 12 years of age and older, when many comedones, papules, and pustules are present.

Pharmacological Properties
*Mechanism of Action*
Trifarotene 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 process by which trifarotene ameliorates acne is unknown.

**DOSAGE AND MODE/ROUTE OF ADMINISTRATION**
Apply a thin layer of Trifarotene (Aklief) Cream to the affected areas once daily (forehead, nose, chin and right and left cheeks) and all affected areas of the trunk once a day, 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.

It is recommended that the physician assesses the continued improvement of the patient after three months of treatment
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.
Patients should be instructed to wash their hands after applying the medicinal product.
Trifarotene (Aklief) Cream is for topical use only. Not for oral, ophthalmic, or intravaginal use.

**CONTRAINDICATIONS**
Hypersensitivity to the active substance or to any of the excipients, pregnancy, women planning a pregnancy

**WARNINGS AND PRECAUTIONS**

Skin Irritation
Patients using Trifarotene (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 Trifarotene (Aklief) Cream, or suspend use temporarily. If severe reactions persist the treatment may be discontinued.
Caution should be exercised if cosmetics or acne medications with desquamative, irritant or drying effects are concomitantly used with the medicinal product, as they may produce additive irritant effects.
Avoid application of Trifarotene (Aklief) to cuts, abrasions, or eczematous or sunburned skin. Use of "waxing" as a depilatory method should be avoided on skin treated with Trifarotene (Aklief) Cream.

Ultraviolet Light and Environmental Exposure
Minimize unprotected exposure to ultraviolet rays (including sunlight and sunlamps) during treatment with Trifarotene (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.
This product contains propylene glycol (E1520) that may cause skin irritation.

Use in Renally Impaired
Trifarotene (Aklief) has not been studied in patients with renal impairment.
Use in Hepatically Impaired Trifarotene (Aklief) has not been studied in patients with hepatic impairment

Use in Geriatrics
Clinical trials of Trifarotene (Aklief) Cream did not include any subjects aged 65 years and over to determine whether they respond differently than younger subjects.

Use in Pediatrics
Safety and effectiveness of Trifarotene (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, a long-term safety trial, and a pharmacokinetic trial. A total of 897 pediatric subjects aged 9 to 17 years received Trifarotene (Aklief) Cream in the clinical trials
Safety and effectiveness of Trifarotene (Aklief)Cream have not been established in pediatric subjects under the age of 9 years.

**FERTILITY, PREGNANCY, AND LACTATION**

**Use in Pregnancy**
Studies in animals with trifarotene by the oral route have shown reproductive toxicity at high systemic exposure.
If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

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 Trifarotene (Aklief) Cream resulted in adverse fetal effects, including fetal deaths and external, visceral, and skeletal malformations.
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.

**Use During 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 Trifarotene (Aklief) Cream and any potential adverse effects on the breastfed infant from Trifarotene (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.
It is unknown whether trifarotene or its metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of Trifarotene/metabolites in milk.
A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Trifarotene (Aklief) herapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
To avoid the risk of ingestion by, and/or contact exposure of, an infant, nursing women should not apply Trifarotene (Aklief) cream to the chest or breast area.
It is unknown whether trifarotene is excreted in human milk following the use of Trifarotene (Aklief) cream.
Oral animal studies have shown that trifarotene is excreted in the milk of lactating rats.
In a two-generation study in rats, no relevant plasma levels were detectable in pups of treated mothers indicating very low exposure during lactation.
No adverse effects due to trifarotene were evident in those animals during development. However, because many drugs are excreted in human milk, precaution should be exercised when Trifarotene (Aklief) is administered to a nursing mother.
To avoid exposure of the infant, application of Trifarotene (Aklief) to the chest should be avoided when used during breast-feeding.

**Fertility**
No human fertility studies were conducted with Aklief.
No effects of trifarotene on fertility were found in rats in reproductive studies of oral administration. After oral administration to dogs, findings of Germ cell degeneration were observed at doses that resulted in systemic exposures 1170 times those in humans at the MRHD of Trifarotene (Aklief) Cream

**INTERACTIONS**
Topical application of Trifarotene (Aklief) cream is not expected to affect the circulating concentrations of oral hormonal contraceptives containing ethinyl estradiol and levonorgestrel.

Effect of other medicinal products on Trifarotene (Aklief) cream
No clinical drug-drug interaction studies were performed to assess effects of other drugs on trifarotene systemic levels.
There is no data on the pharmacodynamic interaction potential of trifarotene. Caution should be exercised if cosmetics or acne medications with desquamative, irritant or drying effects are concomitantly used with the medicinal product, as they may produce additive irritant effects
Model based approach
No clinically significant differences in the pharmacokinetics of trifarotene were predicted when used concomitantly with fluconazole (a moderate CYP2C9 and CYP3A inhibitor).

**ADVERSE DRUG REACTIONS**
Summary of safety profile Local cutaneous reactions such as erythema, scaling, dryness, and stinging/ burning) were collected separately from other adverse events as a measure of local tolerance. These cutaneous reactions are very common and of mild, moderate and severe intensity for up to 39%, 29.7% and 6.2% of patients, respectively on the face. On the trunk, up to 32.9%, 18.9%, 5.2% of patients had mild, moderate and severe reactions respectively. The maximum severity typically occurred at Week 1 for the face, and at Week 2 to 4 for the trunk, and decreased with continued use of the medication.
The most "commonly" reported adverse reactions as described below in Table 1 are application site irritation, application site pruritus and sunburn, occurring in 1.2% to 6.5% of patients treated with Trifarotene (Aklief) cream in clinical studies.
Tabulated summary of adverse reactions:
Adverse reactions reported in the 12-week vehicle-controlled Phase 3 studies in 1220 patients treated with Aklief cream (and for which the rate for Aklief cream exceeds the rate for vehicle cream) are presented in Table 1.

The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to 1<100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Table 1: Adverse reactions

| System Organ Class Frequency Adverse reactions | Frequency | Adverse reactions |
|---|---|---|
| General disorders and administration site conditions | Common | Application site irritation<br>Application site pruritus |
| | Uncommon | Application site pain<br>Application site dryness<br>Application site discolouration<br>Application site erosion<br>Application site rash<br>Application site swelling |
| | Rare | Application site erythema<br>Application site urticaria<br>Application site vesicles |
| Injury, poisoning and procedural complications | Common | Sunburn |
| Skin and subcutaneous tissue disorders | Uncommon | Skin irritation<br>Acne<br>Dermatitis allergic<br>Erythema |
| | Rare | Eczema asteatotic<br>Seborrheic dermatitis<br>Skin burning sensation<br>Skin fissures<br>Skin hyperpigmentation |
| Eye disorders | Rare | Eyelid exfolliation<br>Eyelid oedema |
| Gastrointestinal disorders | Rare | Cheilitis |
| Vascular disorders | Rare | Flushing |

**OVERDOSE AND TREATMENT**
Trifarotene (Aklief) is for once-daily cutaneous use only.
If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, scaling, or skin discomfort may occur. In this event, discontinue use and wait until the skin has recovered.
In case of accidental ingestion, appropriate symptomatic measures should be taken.
Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of vitamin A.

**STORAGE CONDITIONS**
Store at temperatures not exceeding 30°C.

**AVAILABILITY**
30 g Cream in polypropylene (PP) bottle closed with a PP pump/overcap (Box of 1's)
5 g Cream in polyfoil (low density polyethylene /aluminium/ high density polyethylene) tube, with a PP cap (Box of 1's).

**INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL**
Discard 6 months after first opening.
Keep out of the sight and reach of children.

**MARKETING AUTHORIZATION HOLDER**
Galderma Philippines, Inc.
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Philippines

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Taguig, Metro Manila

**CAUTION STATEMENT**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patients must seek medical attention immediately at the first sign of any adverse drug reaction.
For suspected adverse drug reaction, report to the FDA at www.fda.gov.ph and to Galderma Local Safety Officer at philippines.pharmacovigilance@galderma.com

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