SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aklief ®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aklief contains 0.005% w/w Trifarotene.

One gram of cream contains 50 micrograms of Trifarotene

Excipient(s) with known effect
One gram of cream contains:
300 milligrams of propylene glycol and 50 milligrams of ethanol (96%).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream

White and homogenous cream

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

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.

It is recommended that the physician assesses the continued improvement of the patient after three months of treatment.

Special populations

Elderly patients

The safety and efficacy of Aklief in geriatric patients aged 65 years and above have not been established.

Renal and hepatic impairment

Aklief has not been studied in patients with renal and hepatic impairment.

Paediatric population

The safety and efficacy of Aklief in children below 12 years old have not been established.

Method of administration

For cutaneous use only.

Before using the pump for the first time, prime it by pressing down several times until a small amount of medicine is dispensed (up to 10 times maximum). The pump is now ready to use.

Apply a thin layer of Aklief cream to the affected areas of the face (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 pump actuations 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.

Patients should be instructed to avoid contact with the eyes, eyelids, lips and mucous membranes and to wash their hands after applying the medicinal product.

The use of a moisturizer is recommended as needed from the initiation of treatment, while allowing sufficient time before and after the application of Aklief cream to allow the skin to dry.

4.3 Contraindications

- Pregnancy (see section 4.6)
- Women planning a pregnancy
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Erythema, scaling, dryness, and stinging/burning may be experienced with use of Aklief cream (see section 4.8). To mitigate the risk of such reactions, patients should be instructed to use a moisturizer from the initiation of treatment, and, if appropriate, reduce the frequency of application of Aklief cream, or suspend use temporarily. Despite mitigation measures, if severe reactions persist the treatment may be discontinued.

The product should not be applied to cuts, abrasions, eczematous or sunburned skin.

As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with Aklief.

If a reaction suggesting sensitivity to any component of the formula occurs, the use of Aklief should 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.

Aklief should not come into contact with the eyes, eyelids, lips, or mucous membranes. If the product enter the eye, wash immediately and abundantly with luke warm water.

Excessive exposure to sunlight, including sunlamps or phototherapy should be avoided during the treatment. Use of a broad-spectrum, water-resistant sunscreen with a Sun Protection Factor (SPF) of 30 or higher and protective clothing over treated areas is recommended when exposure cannot be avoided.

This medicine contains 300 mg propylene glycol in each gram which is equivalent to 30% w/w. It may cause skin irritation. Aklief also contains 50 mg alcohol (ethanol) in each gram which is equivalent to 5% w/w. It may cause burning sensation on damaged skin.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Aklief cream on other medicinal products

A clinical drug-drug interaction study has shown that topical application of trifarotene did not affect the circulating concentrations of hormonal contraceptives (ethinyl estradiol and levonorgestrel) administered by oral route.

Effect of other medicinal products on Aklief cream

No clinical drug-drug interaction studies were performed to assess effects of other drugs on trifarotene systemic levels (see section 5.2).

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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Pregnancy

Aklief is contraindicated (see section 4.3) during pregnancy or in women planning a pregnancy.

Studies in animals with trifarotene by the oral route have shown reproductive toxicity at high systemic exposure (see section 5.3).

If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Breast-feeding

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 (for details see 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Aklief therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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. However, after oral administration to dogs, findings of *Germ cell degeneration* were observed, see section 5.3.

4.7 Effects on ability to drive and use machines

Aklief has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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 (see section 4.4).

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 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**
General disorders and administration site conditions	Common	Application site irritation Application site pruritus
	Uncommon	Application site pain Application site dryness Application site discolouration Application site erosion Application site rash Application site swelling
	Rare	Application site erythema Application site urticaria Application site vesicles
Injury, poisoning and procedural complications	Common	Sunburn
Skin and subcutaneous tissue disorders	Uncommon	Skin irritation Acne Dermatitis allergic Erythema
	Rare	Eczema asteatotic Seborrheic dermatitis Skin burning sensation

System Organ Class	Frequency	Adverse reactions
		Skin fissures Skin hyperpigmentation
Eye disorders	Rare	Eyelid exfolliation Eyelid oedema
Gastrointestinal disorders	Rare	Cheilitis
Vascular disorders	Rare	Flushing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoids for topical use in acne, ATC code: D10AD06

Mechanism of action

Aklief cream contains 50 micrograms (mcg/g) (w/w) trifarotene, which is a chemically stable, terphenyl acid derivative with retinoid-like activity. It is a potent RARγ agonist (retinoid acid receptor γ agonist), characterized by its high specificity to this receptor over RAR$_\alpha$ & RAR$_\beta$ (50- and 8-fold, respectively, with no Retinoid X Receptor (RXR) activity).

In addition, trifarotene modulates retinoid target genes (differentiation and inflammatory processes) in immortalized keratinocytes and reconstructed epidermis.

Pharmacodynamic effects

Trifarotene has demonstrated, in the Rhino-mouse model, marked comedolytic activity with the reduction in the comedone count and marked increased epidermis thickness. In this model, trifarotene produced the same comedolytic effect as other known retinoids, at about 10 times lower dose.

Trifarotene has also shown anti-inflammatory and depigmenting activities.

Clinical efficacy and safety

Aklief cream applied once daily in the evening was evaluated for 12 weeks in 2 randomized, multi-center, parallel group, double-blind, vehicle-controlled studies of identical design. They were conducted in a total of 2420 patients aged, 9 years and older, with moderate facial and truncal acne vulgaris.

Acne severity was evaluated using the 5-point Investigator's Global Assessment (IGA) scale for the face and Physician's Global Assessment (PGA) for the trunk, with moderate acne vulgaris defined as a score of Grade 3-Moderate (see Table 2).

Table 2: Investigator's Global Assessment and Physician's Global Assessment Scales

0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

There were three identical co-primary efficacy endpoints in both pivotal studies 1) the success rate based on the IGA and PGA outcome (percentage of subjects "clear" and "almost clear" and with at least a 2-grade change from baseline) and absolute and percentage change from baseline in 2) inflammatory and 3) non-inflammatory lesion counts at Week 12.

Overall, 87% of subjects were Caucasian and 55% were female. Thirty four (1.4%) subjects were 9 to 11 years of age, 1128 (47%) subjects were 12 to 17 years and 1258 (52%) subjects were 18 years and older. All patients had moderate acne vulgaris on the face and 99% 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. Additionally subjects had 21 to 305 (average 52) non-inflammatory lesions on the face and 0 to 260 (average 46) on the trunk.

The IGA and PGA success rates, mean absolute, and percent reduction in acne lesion counts from baseline after 12 weeks of treatment are presented in the following tables:

Table 3: Facial Acne Improvement in Investigator's Global Assessment and Change in Lesion Counts at Week 12 (Intent-to-Treat; Multiple Imputation)

Primary Efficacy Endpoints	**Study 18251**		**Study 18252**	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	N= 612	N= 596	N= 602	N=610
IGA Success Rate (%) (At least 2-grade improvement and IGA of "Clear" (0) or "Almost Clear" (1))	29.4	19.5	42.3	25.7

Primary Efficacy Endpoints	**Study 18251**		**Study 18252**	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	N= 612	N= 596	N= 602	N=610
Percent difference from vehicle (95% CI)	9.8 (4.8, 14.8) *p < 0.001*	-	16.6 (11.3, 22.0) *p < 0.001*	-
Inflammatory Lesions Mean Absolute Change from Baseline				
LS Mean (SE)	-19.0 (0.50)	-15.4 (0.51)	-24.2 (0.51)	-18.7 (0.51)
LS Mean Difference from vehicle (95% CI)	-3.6 (-4.9,- 2.2) *p < 0.001*	-	-5.6 (-6.9,- 4.3) *p < 0.001*	-
Mean Percent Change from Baseline (%)				
Mean (SE)	15.7 (0.52)	19.3 (0.64)	12.0 (0.51)	17.6 (0.58)
Mean Percent Change from Baseline	-54.4 *p < 0.001 vs. Vehicle*	-44.8	-66.2 *p < 0.001 vs. Vehicle*	-51.2
Non-inflammatory Lesions Mean Absolute change from Baseline				
LS Mean (SE)	-25.0 (0.87)	-17.9 (0.87)	-30.1 (0.71)	-21.6 (0.71)
LS Mean Difference from vehicle (95% CI)	-7.1 (-9.4,- 4.8) *p < 0.001*	-	-8.5 (-10.3,-6.6) *p < 0.001*	-
Mean Percent Change from Baseline (%)				
Mean (SE)	28.0 (1.08)	34.5 (1.22)	20.6 (0.71)	28.9 (0.97)
Mean Percent Change from Baseline	-49.7 *p < 0.001 vs. Vehicle*	-35.7	-57.7 *p < 0.001 vs. Vehicle*	-43.9

Table 4: Truncal Acne Improvement in Physician's Global Assessment and Change in Lesion Counts at Week 12 (Intent-to-Treat on the Trunk, Multiple Imputation):

Secondary Endpoints	**Study 18251**		**Study 18252**	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	N= 600	N=585	N= 598	N=609
PGA Success Rate (%) (At least 2-grade improvement and PGA of "Clear" (0) or "Almost Clear" (1))	35.7	25.0	42.6	29.9
Percent difference from vehicle (95% CI)	10.7 (5.4, 16.1) *p < 0.001*	-	12.7 (7.2, 18.2) *p < 0.001*	-

Secondary Endpoints	**Study 18251**		**Study 18252**	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	N= 600	N=585	N= 598	N=609
Inflammatory Lesions **Mean Absolute Change from Baseline**				
LS Mean (SE)	-21.4 (0.54)	-18.8 (0.55)	-25.5 (0.59)	-19.8 (0.58)
LS Mean Difference from vehicle (95% CI)	-2.5 (-4.0,- 1.1) *p< 0.001*	-	-5.7 (-7.2,- 4.2) *p< 0.001*	-
Mean Percent Change from Baseline (%)				
Mean (SE)	15.9 (0.60)	17.9 (0.64)	13.5 (0.57)	18.8 (0.71)
Mean Percent Change from Baseline	-57.4 *p < 0.001 vs. Vehicle*	-50.0	-65.4 *p < 0.001 vs. Vehicle*	-51.1
Non-inflammatory Lesions **Mean Absolute Change from Baseline**				
LS Mean (SE)	-21.9 (0.93)	-17.8 (0.94)	-25.9 (0.67)	-20.8 (0.66)
LS Mean Difference from vehicle (95% CI)	-4.1 (-6.6,- 1.7) *p= 0.001*	-	-5.0 (-6.8,- 3.3) *p < 0.001*	-
Mean Percent Change from Baseline (%)				
Mean (SE)	24.5 (1.01)	29.4 (1.17)	20.5 (0.78)	24.5 (0.77)
Mean Percent Change from Baseline	-49.1 *p < 0.001 vs. Vehicle*	-40.3	-55.2 *p < 0.001 vs. Vehicle*	-45.1

Paediatric population

Age group 9 to 11 years: In the phase 3 studies a total of only 34 children of this age group were included - 19 of them in study 18251 and 15 in study 18252. In this age group, patient number was low and efficacy could not be demonstrated

Age group 12 to 17 years: In the phase 3 studies a total of 1128 children aged 12 to 17 years with moderate acne vulgaris were included: 573 of them in study 18251 and 555 children in study 18252.

The IGA and PGA success rates, mean absolute, and percent reduction in acne lesion counts from baseline after 12 weeks of treatment are presented in the following tables:

Table 5: Facial Acne Improvement in Investigator's Global Assessments and Change in Lesion Counts at Week 12 in 12 to 17 years of age (Intent-to-Treat population; Multiple Imputation).

Primary Efficacy Endpoints	**Study 18251**		**Study 18252**	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	(n= 304)	(n=269)	(n= 267)	(n=288)
IGA Success Rate (%) **At least 2-grade improvement and IGA of "Clear" (0) or "Almost Clear" (1)**	25.6	14.7	35.8	20.4
Percent difference in Success rate from the vehicle (95% CI)	10.9 (4.3, 17.6) *p < 0.001*	-	15.4 (7.9, 23.0) *p < 0.001*	-
Inflammatory Lesions **Mean Absolute Change from Baseline**	-18.7	-14.8	-24.0	-18.7
Mean difference from the vehicle (95% CI)	-3.8 (-6.5,- 1.2) *p < 0.001*	-	-5.3 (-8.1,- 2.6) *p < 0.001*	-
Non-inflammatory Lesions **Mean Absolute Change from Baseline**	-26.5	-16.8	-33.8	-22.8
Mean difference from the vehicle (95% CI)	-9.6 (-13.8,- 5.4) *p < 0.001*	-	-11.0 (-15.2,- 6.8) *p < 0.001*	-

Table 6: Truncal Acne Improvement in Physician's Global Assessments and Change in Lesion Counts at Week 12 in 12 to 17 years of age (Intent-to-Treat truncal population; Multiple Imputation).

Secondary Endpoints	**Study 18251**		**Study 18252**	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	(n= 302)	(n=269)	(n= 267)	(n=288)
PGA Success Rate (%) **At least 2-grade improvement and PGA of "Clear" (0) or "Almost Clear" (1)**	31.8	21.0	38.7	25.8
Percent difference in Success rate from the vehicle (95% CI)	10.8 (3.5, 18.1) *p < 0.001*	-	12.9 (5.0, 20.8) *p < 0.001*	-

Secondary Endpoints	Study 18251		Study 18252	
	AKLIEF cream	Vehicle cream	AKLIEF cream	Vehicle cream
	(n= 302)	(n=269)	(n= 267)	(n=288)
Inflammatory Lesions **Mean Absolute Change from Baseline**	-21.4	-18.0	-25.4	-19.2
Mean difference from the vehicle (95% CI)	-3.4 (-6.3, -0.5) *p < 0.001*	-	-6.2 (-9.2,- 3.3) *p < 0.001*	-
Non-inflammatory Lesions **Mean Absolute Change from Baseline**	-22.2	-17.2	-25.7	-20.1
Mean difference from the vehicle (95% CI)	-5.0 (-9.1, -0.8) *p < 0.001*	-	-5.7 (-9.1,-2.2) *p < 0.001*	-

Long-term efficacy

In **Study 3**, a one-year open label safety study of 453 patients, 9 years and older, with moderate facial and truncal acne vulgaris, Aklief cream demonstrated a clinically meaningful improvement with IGA and PGA success rates increasing:

- from 26.6% at Week 12 visit to 65.1% at Week 52 visit for the face and
- from 38.6% at Week 12 visit to 66.9% at Week 52 visit for the trunk, respectively.

IGA and PGA success experienced by the same subject increased from 22.0% at Week 12 to 57.9% at Week 52.

START study

The effect of Aklief cream on acne scarring during the treatment of acne vulgaris was investigated in the START study. The START study is a multi-center, randomized, double-blind, vehicle-controlled study with intra-individual comparison (right half-face versus left half-face) evaluating atrophic scar counts over 24 weeks of treatment.

The START study consisted mainly of subjects with moderate acne at baseline (over 90% of subjects with IGA score of 3). The 121 subjects enrolled in the study presented atrophic acne scars of mostly mild and moderate severity as assessed by the Investigator Scar Global Assessment on both halves of the face.

The median age for all subjects was 22 years (with a minimum of 17 years, maximum of 34 years). The majority of subjects (102 [84.3%]) were adults (≥18 years), female (88 [72.7%] subjects), white (97 [80.2%], and non-Hispanic or Latino (95 [78.5%]).

The primary efficacy endpoint was the absolute change from baseline in total atrophic acne scar count per half-face at Week 24. Total number of atrophic acne scars significantly decreased with Aklief compared to vehicle (see Table 7).

Table 7: Change from Baseline in Total Atrophic Acne Scar Count at Week 24 by Imputing Missing Data using Multiple Imputation under the Assumption of Missing At Random (ITT Population)

Aklief (N=121)		Vehicle (N=121)		Treatment Difference (N=121)		
Mean Baseline Scar Count	**Mean Change from Baseline**	**Mean Baseline Scar Count**	**Mean Change from Baseline**	**Mean (SE) of Difference in Change from Baseline**	**95% Confidence Interval**	**p-value**
11.4	-5.9	11.6	-2.7	-3.2 (0.60)	-4.4, -2.0	<0.0001

Descriptive statistics showed that trifarotene performed numerically better in 2-4 mm compared to >4 mm atrophic scars.

5.2 Pharmacokinetic properties

Absorption

The absorption of trifarotene from Aklief cream was evaluated in adult and paediatric (10-17 y.o.) subjects with acne vulgaris. Subjects were treated once daily for 30 days with 2 grams/day of Aklief applied on the face, shoulders, chest, and upper back.

Overall, systemic exposure levels were low and similar between adults and paediatric populations.

After 4 weeks treatment, seven of nineteen (37%) adult subjects had quantifiable trifarotene plasma levels. Cmax ranged from below the limit of quantification (LOQ <5 pg/mL) to 10 pg/mL and $AUC_{0\text{-}24h}$ ranged from 75 to 104 pg.hr/mL.

Three of the seventeen (18%) of paediatric subjects presented quantifiable systemic exposure. Cmax ranged from below the limit of quantification (LOQ <5 pg/mL) to 9 pg/mL and $AUC_{0\text{-}24h}$ ranged from 89 to 106 pg.hr/mL.

Steady state conditions were achieved in both adult and paediatric subjects following 2 weeks of topical administration. No drug accumulation is expected with long-term use.

Distribution

Trifarotene penetrates into the skin with an exponential distribution from the stratum corneum to the epidermis and dermis.

An in vitro study demonstrated that trifarotene is greater than 99.9% bound to plasma proteins. No significant binding of trifarotene to erythrocytes was observed.

Biotransformation

In vitro studies using human hepatic microsomes and recombinant CYP450 enzymes have shown that trifarotene is primarily metabolized by CYP2C9, CYP3A4, CYP2C8 and at lesser extent by CYP2B6.

Pharmacokinetic drug interaction potential

In vitro studies show that Aklief cream at the concentrations achieved systemically after topical administration did not inhibit the CYP450 isoenzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, and did not induce CYP1A2, 2B6, or 3A4.

In vitro studies have shown that Aklief cream at the concentrations achieved systemically after topical administration did not inhibit either MATE, OATP, OAT or OCT uptake transporters or BCRP, PgP, BSEP or MPR efflux transporters.

5.3 Preclinical safety data

Note: the animal multiples of human systemic exposure calculations were based on Area Under the Curve (AUC) comparisons for a topical human dose of 2 g of Aklief Cream, applied once daily.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated oral dose toxicity, genotoxicity, or carcinogenic potential.

In dermal repeat-dose toxicity studies in minipigs for up to 9 months, systemic exposure to trifarotene was very low, generally below the limit of quantification. There were no systemic effects and the only noteworthy finding consisted of reversible skin irritation at the application sites.

In animal reproduction studies, oral administration of trifarotene in pregnant rats and rabbits during organogenesis was teratogenic and embryotoxic at exposures (AUC) that were 1614 to 18245-times and 800 to 4622-times those observed in humans at the maximum recommended human dose (MRHD) of 2 g.

Trifarotene was not teratogenic in rats and rabbits at systemic exposures corresponding to 534 and 98-times respectively those observed in humans.

Trifarotene had no effects on pre- and post-natal development in rats, up to the highest oral doses tested which corresponded to systemic exposures (AUC) 595 to 1877-times higher than those observed in humans.

Trifarotene showed no adverse effects on fertility in rats administered orally at exposures of approximately 1754 (males) and 1877 (females) times the 2 g dose in humans. However, after oral administration to dogs, *Germ cell degeneration* with pyknotic/apoptotic germ cells was evident from the lowest dose tested of 0.2mg/kg/day corresponding to a systemic exposure 1170 times higher than those observed in humans. All animals with this finding also showed *hypospermatogenesis and debris in the epididymides.* The findings did not completely recover after 8 weeks, suggesting an extended and possibly chronic effect. As these effects were noted also at the lowest dose tested, the relevance of the findings for lower doses is unknown.

Oral study in rats have shown trifarotene and/or related metabolites are excreted into maternal milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Medium-chain triglycerides
Ethanol (96%)
Copolymer of acrylamide and sodium acryloyldimethyltaurate (40% dispersion)
Cyclomethicone 5
Phenoxyethanol
Allantoin
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening: use within 6 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

[Airless pump]

[15g; 30g; 75g]

15g - Polypropylene (PP) bottle with HDPE piston and a PP closure.
30g; 75g – VLDPE bottle with HDPE piston and a PP closure.

Pack sizes: 1 bottle of 15, 30 or 75 g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Manufacturer

Laboratoires Galderma, Z.I. Montdesir 74 540 Alby-sur-Cheran, France

8 Registration holder

A.M.I. Medical Technologies Limited, Hanagar 22, Hod Hasharon, 4501317, Israel

Registration number: 176-48-37123-99

Revised in May 2025.