Taiwan Food and Drug Administration

Assessment Report

Trade Name：艾克痘乳膏 / Aklief 50 μg/g Cream

Active Ingredient：Trifarotene

License Number：MOHW-PI 028310

Applicant：香港商高德美有限公司台灣分公司

Approval Date：2022.7.8

Indication：
適用於成人與 12 歲以上青少年病人尋常性痤瘡的皮膚治療。

Aklief is indicated for the topical treatment of acne vulgaris of the in patients from 12 years of age and older.

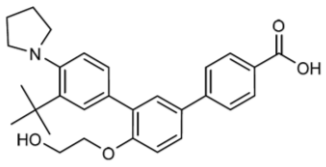
1. Background Information

Trade Name	艾克痘乳膏 / Aklief 50μg/g Cream
Active Ingredient(s)	Trifarotene
Applicant	香港商高德美有限公司台灣分公司
Dosage Form & Strengths	乳膏劑 0.05μg/g
Indication	適用於成人與 12 歲以上青少年病人尋常性痤瘡的皮膚治療。 Aklief is indicated for the topical treatment of acne vulgaris in patients from 12 years of age and older.
Posology	每天晚上一次，清潔皮膚並乾燥後，在臉部和/或軀幹的患處塗抹薄薄一層的Aklief乳膏。建議醫師在治療三個月後評估病人持續改善的情況。 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
Pharmacological Category **ATC Code**	D10AD06

2. Summary Report

Drug Substance

The drug substance, trifarotene, is chemically designated as 4-{3-[3-tert-butyl-4-(pyrrolidin-1-yl)phenyl]-4-(2-hydroxyethoxy)phenyl} benzoic acid and has the following structure:



It is a white to off-white to slightly yellow powder. The molecular formula and the molecular weight are $C_{29}H_{33}NO_4$ and 459.59 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of trifarotene has been confirmed by elemental analysis, IR, NMR and mass spectrometry.

The drug substance specification includes tests for appearance, identification, color of the

solution, clarity of the solution, sulfated ash, water content, related substances, residual solvents and assay.

Drug Product

Aklief 50 μg/g Cream is a white cream filled into an airless bottle system or a polyfoil tube. Each gram contains 50 μg trifarotene. The excipients used in the drug product formulation comply with the compendial monographs.

The drug product specification includes characteristics, identification, mean fill weight, pH, viscosity, impurities, assay and microbiological quality. Analytical methods are described well and validated.

Stability studies of the drug products under long term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Nonclinical Pharmacology/Toxicology Evaluation

In vitro, trifarotene is a potent RARγ agonist with high selectivity to receptor γ over RARα and RARβ and with no RXR activity. *In vitro* cell-based assays using human immortalized keratinocytes, reconstructed epidermis, and skin explants had shown that trifarotene modulated retinoid-target genes for keratinization, metabolism, adhesion, differentiation, and inflammation processes.

In an *in vivo* rhino mouse model, topical use of trifarotene Cream showed a dose-dependent comedolytic activity at the concentration of 0.01%. Moreover, topical application of trifarotene in mice demonstrated anti-inflammatory and de-pigmentation effects. Strong de-pigmentation and anti-pigmentation activity along with a marked to severe epidermal hyperplasia were shown at 0.003%.

In vitro hERG assay showed that the IC50 values of trifarotene were 500,000 times higher than the highest Cmax in humans. Overall, a standard battery of safety pharmacology studies of trifarotene did not reveal potential risk on the vital organ functions at doses corresponding to the levels much higher than the MRHD.

Repeated-dose dermal toxicity studies were conducted in the mice for up to 13 weeks and in the minipig for up to 9 months. In a 13-week mice study, doses up to 0.2 mg/kg/day resulted in dose-related local skin reactions, including inflammatory changes at the application sites at all doses. Microscopically, the main effects were noted in the skin, stomach, and bones. In a 9-month minipig study, topical administration of trifarotene at doses up to 0.025 mg/kg/day was well-tolerated and showed no systemic toxicity. The only treatment-related effects were

reversible, dose-related skin irritation reactions at the application sites. The NOAELs were not determined in these dermal studies.

Repeated-dose oral toxicity studies were performed in rats for up to 26 weeks and in dogs for up to 9 months. In rats, the treatment-related toxicities were shown in the skin, bones, stifle joint, and stomach with a trend to recovery. In the 9-month oral study in the dog, treatment-related histopathological changes were found in the testes, epididymides, skin, and ears, and these changes were mostly reversible except the finding in the testes at the highest dose tested. Although no NOAEL could be determined for the male dogs in the 9-month study, the NOAEL values in the abovementioned studies provided quite high safety margins for the clinical dose in terms of AUC.

Trifarotene was negative in a battery of genotoxicity studies and not carcinogenic in the 2-year dermal study in mice and the oral study in rats.

A standard battery of DART studies was conducted in rats or rabbits by oral administration of trifarotene. No effect on FEED and PPND parameters was observed in rats. However, trifarotene was teratogenic when tested in rats or rabbits. In a non-GLP juvenile dog study, oral dosing of trifarotene for 4 weeks showed no obvious treatment-related adverse effects. The NOAEL values of DART and juvenile dog studies all provided quite high safety margins in terms of AUC.

Lastly, although trifarotene induced dose-related skin irritation in all species tested, Trifarotene 50 µg/g Cream was non-irritating to the eye in rabbits and non-sensitizing to the skin in guinea pigs.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The absorption of trifarotene cream was evaluated in adult and paediatric (10-17 years old) 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. C_{max} 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. C_{max} 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.

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.

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.

Trifarotene is primarily excreted by the feces. The terminal half-life ranged from 2 to 9 hours.

2.3.2 Interaction Studies

In vitro studies show that trifarotene 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 also have shown that trifarotene 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.

2.3.3 Special Populations

Trifarotene cream also has not been studied in patients with renal and hepatic impairment. The safety and efficacy of trifarotene cream in children below 12 years old have not been established, either.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two identically-designed, Phase III, randomized, double-blind, multi-national, multi-center, vehicle-control pivotal studies ([18251] and [18252]) have been provided to support the efficacy of Aklief (trifarotene) 50 μg/g cream in the treatment of acne vulgaris.

For both studies, the co-primary endpoints were IGA success rate, absolute change in facial inflammatory lesion count from baseline to Week 12, and absolute change from in facial non-inflammatory lesion count from baseline to Week 12. The co-secondary endpoints were similar to the co-primary endpoints but were evaluated for truncal acne.

Table 2.4.1-1 and Table 2.4.1-2 present the results of the co-primary endpoints evaluated on the face and the co-secondary endpoints evaluated on the trunk, respectively. All endpoints

were statistically significant with p-value less than 0.001 for both studies.

Table 2.4.1-1 Results for co-primary endpoints (Face) at Week 12 for ITT population

	Study [18251]			Study [18252]		
	Aklief (N = 612)	Vehicle (N = 596)	Trt effect (p-value)	Aklief (N = 602)	Vehicle (N = 610)	Trt effect (95% CI) p-value
IGA success (face)	29.4%	19.5%	9.8% (< 0.001)	42.3%	25.7%	16.6% (< 0.001)
Inflammatory lesions Change, LS mean	-19.0	-15.4	-3.6 (p < 0.001)	-24.2	-18.7	-5.6 (p < 0.001)
Non-Inflammatory lesions Change, LS mean	-25.0	-17.9	-7.1 (p < 0.001)	-30.1	-21.6	-8.5 (p < 0.001)

Table 2.4.1-2 Results for co-secondary endpoints (Trunk) at Week 12 for ITT population

	Study [18251]			Study [18252]		
	Aklief (N = 612)	Vehicle (N = 596)	Trt effect (95% CI) p-value	Aklief (N = 602)	Vehicle (N = 610)	Trt effect (95% CI) p-value
PGA success (trunk)	35.7%	25.0%	10.7% (< 0.001)	42.6%	29.9%	12.7% (< 0.001)
Inflammatory lesions Change, LS mean	-21.4	-18.8	-2.5 (p < 0.001)	-25.5	-19.8	-5.7 (p < 0.001)
Non-Inflammatory lesions Change, LS mean	-21.9	-17.8	-4.1 (p < 0.001)	-25.9	-20.8	-5.0 (p < 0.001)

In conclusion, the submitted data provide sufficient evidence to support the efficacy of trifarotene 50 μg/g cream for the treatment of acne vulgaris in the population age 12 years and older.

2.4.2 Safety Results

In Studies 18251, 18252, and 18250, 1220 subjects were treated once daily for up to 12 weeks and 453 subjects were treated once daily for up to 1 year. The most common adverse reactions were application site irritation, application site pruritus, and sunburn. In the open-label long-term non-comparative Study 18250, 16 (3.5%) subjects had AEs leading to treatment discontinuation. The most common AEs leading to discontinuation was application site irritation.

Skin irritation symptoms and signs including erythema, scaling, dryness, and stinging/burning were assessed in the two 12-week Phase 3 Studies 18251 and 18252 at Baseline and at least one post-Baseline visit. Local tolerability on the face in subjects treated with Aklief worsened for any of the symptoms/signs 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 for the trunk, and decreased thereafter.

2.5 Bridging Study Evaluation

A pharmacokinetic study to compare the systemic exposure of trifarotene in healthy subjects of Japanese and non-Japanese after repeated once-daily topical application (2 g) for 29 days of trifarotene 100 μg/g cream was conducted. The results showed that C_{max} and AUC were 8.3 pg/mL and 100 pg*h/mL, respectively, in Japanese, and were 9.7 pg/mL and 117 pg*h/mL in non-Japanese at Day 29. In conclusion, no significant impact of ethnicity was observed on trifarotene systemic exposure parameters.

In Phase 3 Studies 18251 and 18252, only 25 (2.0%) subjects of Aklief Group and 38 (3.2%) subjects of Vehicle Group were enrolled from Asia. Based on the limited clinical data, the efficacy results of Asian population were generally consistent with that of Overall population. No additional safety signal was identified in Asian population.

2.6 Conclusion

This multidisciplinary review recommends approval for Aklief 50μg/g Cream (Trifarotene) for the indication of topical treatment of acne vulgaris in patients 12 years of age and older.

3. Post-Marketing Requirements

No post-marketing requirement is needed.