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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Aklief

International non-proprietary name: trifarotene

Pharmaceutical form: cream

Dosage strength: 50 µg/g

Route(s) of administration: cutaneous use

Marketing Authorisation Holder: Galderma SA

Marketing Authorisation No.: 67632

Decision and Decision date: approved on 16 December 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ADR	Adverse drug reaction
AEs	Adverse events
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast Cancer Resistance Protein
C _{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HPLC	High Pressure Liquid Chromatography
HPLC-MS/MS	High Pressure Liquid Chromatography-Mass Spectrometry
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IR	Infrared
LDPE	Low density polyethylene
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human daily dose
N/A	Not applicable
NMR	Nuclear magnetic resonance
NO(A)EL	No Observed (Adverse) Effect Level
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RAR	Retinoic acid receptor
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UV	Ultraviolet Spectrometry
w/w	Weight by weight

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance trifarotene of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Aklief is indicated for the cutaneous treatment of *Acne Vulgaris* of the face and/or trunk in patients from 9 years of age and older, when many comedones, papules and pustules are present.

2.2.2 Approved Indication

Aklief is indicated for the topical treatment of moderate* acne vulgaris on the face and/or torso in patients aged 12 and over, if more than half the surface is affected, in the presence of numerous comedones, papules and pustules.

* See section *Properties/ Effects*, Table 2

2.2.3 Requested Dosage

Once daily application in the evening of a thin layer of cream to the affected areas of the face and/or trunk. The duration of the treatment should be determined by the doctor based on the clinical condition.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	01 July 2019
Formal control completed	16 July 2019
List of Questions (LoQ)	13 November 2019
Answers to LoQ	17 February 2020
Predecision	11 May 2020
Answers to Predecision	1 July 2020
Labelling corrections	25 September 2020
Answers to Labelling corrections:	22 October 2020
Final Decision	16 December 2020
Decision	approval

3 Medical Context

Acne vulgaris is a common skin disease: in Western industrialised countries its prevalence in adolescents is estimated to be 50% to 95% overall, and still as high as 20% - 35% when only moderate and severe forms are considered.

It is a polymorphic chronic inflammatory disease of the pilosebaceous follicles of the skin. Acne vulgaris nearly always affects the face (99%) and also commonly affects the back (60%) and chest (15%), i.e. the trunk. Clinically, it presents with open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules and nodules. Seborrhoea is a frequent feature. Scarring and post-inflammatory hyperpigmentation are frequently seen sequelae. Acne vulgaris can wax and wane in severity and tends to relapse after treatment discontinuation. Acne vulgaris is mainly a disease of adolescence and triggered in children by the initiation of androgen production. It may begin as early as age 7-9 and usually subsides after the end of growth, but may also persist beyond teen age in a significant proportion of individuals.

4 Quality Aspects

4.1 Drug Substance

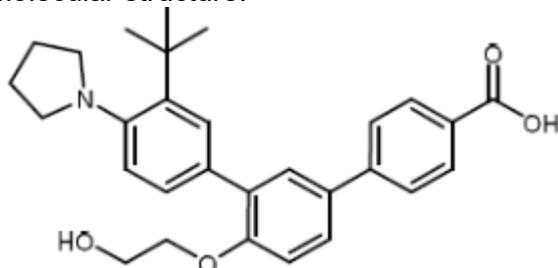
INN: Trifarotene

Chemical name: 4-{3-[3-tert-butyl-4-(pyrrolidin-1-yl)phenyl]-4-(2-hydroxyethoxy)phenyl} benzoic acid

Molecular formula: $C_{29}H_{33}NO_4$

Molecular mass: 459.59 g mol⁻¹

Molecular structure:



Trifarotene

Physico-chemical properties: Trifarotene is a white to slightly yellow powder, practically insoluble over the physiological pH range. It does not contain a chiral centre. Trifarotene shows polymorphism, and the two polymorphic forms that can be obtained through the synthesis process, forms I and II, have similar properties.

Synthesis: The process consists of a chemical synthesis. A convergent synthesis is performed to obtain final isolated intermediates. These are coupled in the last step of synthesis, finally producing trifarotene. The definition of starting materials is consistent with the requirements and/or recommendations provided in ICH Q7, ICH Q11, and CPMP Guidance CPMP/QWP/130/96. It is also in line with the EMA Scientific Advice of 26 June 2014.

Structure elucidation: The chemical structure of trifarotene is deduced from its route of synthesis and was confirmed by elemental analysis, IR, NMR and mass spectrometry.

Specification: appearance, identification (IR, HPLC), colour and clarity of solution, sulphated ash, water content, related impurities (HPLC), residual solvents, assay (HPLC). The omission of some tests in the specifications is justified.

Stability: The bulk drug substance is packaged in double LDPE bags placed in a secondary packaging. A stability study was carried out according to the current guideline recommendations. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug Product

Description and composition: Trifarotene is presented in a semi-solid dosage form defined as a cream and is completely solubilised. The drug product consists of a white cream filled into an airless bottle system. The drug product contains trifarotene 50 µg/g of cream (0.005% w/w). The maximum daily dose, as proposed on the label, corresponds to 2 g of drug product (trifarotene 50 µg/g cream), i.e. 100 µg of trifarotene drug substance applied to the skin.

The excipients are purified water, propylene glycol, allantoin, medium-chain triglycerides, phenoxyethanol, cyclomethicone, copolymer of acrylamide and sodium acryloyldimethyltaurate (acrylamide / sodium acryloyldimethyltaurate copolymer, dispersion 40% in isohexadecane, polysorbate 80, sorbitan oleate), ethanol 96 %. The excipient phenoxyethanol is used as a solvent and as an antimicrobial preservative.

Pharmaceutical development: The pharmaceutical development is presented in sufficient detail to support the proposed cream formulation composition and scale-up activities.

Manufacture: The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

Specification: The drug product specification covers relevant physico-chemical characteristics. The drug product specification includes the following parameters: appearance white and homogeneous, trifarotene identification by HPLC and UV, phenoxyethanol identification by HPLC, assay of trifarotene and the preservative (phenoxyethanol), pH, impurities, apparent viscosity, minimum fill and microbial examination. The proposed limits are acceptable. The omission of certain tests is justified. The control methods are validated according to ICH guidelines. Batch data show consistent quality of the drug product.

Container Closure System: This consists of a polypropylene (PP) bottle closed with a PP pump/overcap. The bottle sizes proposed for commercial use are 15, 30 and 75 g. The airless bottle primary packaging is adequate to protect and deliver the drug product, considering that the pump is used to facilitate its application.

Stability: The conditions used in the stability studies are according to the ICH stability guideline. The applicant has performed long-term and accelerated stability, photostability, thermal cycling stability and in-use stability studies. In addition to the product specification, packaging integrity, weight loss, functional testing and antimicrobial effectiveness testing were also tested. The proposed shelf-life and in-use shelf-life are acceptable.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical Aspects

Pivotal safety pharmacology and toxicity studies were conducted according to GLP.

Pharmacology

Trifarotene had a 50- and 8-fold higher selectivity for the retinoic acid receptors (RAR γ) compared to RAR α and RAR β , respectively, with an EC₅₀ of 7.7 nM. The phase I metabolite CD09986 had an RAR activity comparable to the parent compound. Functional activity was shown in human keratinocytes in a reconstituted human epidermis model and a human skin explant model. *In vivo*, trifarotene showed comedolytic activity and increased epidermal thickness and transdermal water loss in the rhino mouse model.

The acute irritation potential and the depigmenting and anti-pigmenting activity in mice was higher than that seen with other retinoids. Trifarotene showed anti-inflammatory activity in a murine ear oedema model. Additional off-target activity was not evaluated, which is considered acceptable in light of the low systemic exposure following dermal application in humans.

No safety pharmacology hazard was identified for the clinical use of trifarotene 50 μ g/g cream.

Pharmacodynamic drug interaction studies were not conducted, which is acceptable based on the very low plasma concentrations of trifarotene and its metabolites.

Pharmacokinetics

Bioanalytical HPLC-MS/MS methods were validated for quantification of trifarotene in the plasma of mice, rats, rabbits, dogs, and minipigs.

In an *in vitro* murine skin assay, trifarotene penetrated but did not pass the skin. Absorption was assessed in rats, dogs, and minipigs. Exposure was 3.3 to 5.6-fold higher in female rats compared to males for all routes. There were no gender-related differences in dogs. All species showed low to moderate clearance and a high volume of distribution after intravenous (i.v.) and/or oral administration. Elimination half-life ($t_{1/2}$) was ~3 to 6.5 hours in animals, similar to that in humans. Bioavailability was ~5% after dermal application in rats. Toxicokinetic data for trifarotene showed a slightly less than or dose-proportional exposure increase and no accumulation > 2.5-fold.

There was no preferential blood cell binding or accumulation in pigmented tissues or in brain. Plasma protein binding was \geq 99.7% in all animal species and humans. Radioactivity distributed widely into tissues after oral and i.v. administration of [¹⁴C]- trifarotene to rats. [¹⁴C]- trifarotene and its metabolites crossed the placenta in pregnant rabbits and were detected in the milk of lactating rats. Trifarotene was metabolised intensively *in vitro* in hepatocytes of rats, rabbits, minipigs, monkeys and humans, but only to a small extent in dog hepatocytes (35%) and, in rats and dogs, in liver microsomes (42 and 17%, respectively). No human-specific metabolite was identified. Trifarotene was not metabolised by human keratinocytes *in vitro*. Trifarotene was the major circulating component after oral or i.v. administration in rats and dogs. Three of the five human Phase I *in vitro* metabolites were identified in the plasma of rats, pregnant rabbits and dogs, two of which were quantified in humans after suprathreshold dermal administration. Faeces was the main excretion route in rats, dogs, and humans.

Toxicology

Based on the ADME profile and pharmacological activity, the selected animal species are considered appropriate. Toxicity was assessed after repeated dermal administration in mice up to 13 weeks and minipigs up to 36 weeks, and, after oral dosing, up to 26 weeks in rats and 9 months in dogs. While a single dermal administration of trifarotene was well tolerated, a single i.v. dose resulted in adverse bone effects and kidney mineralisation at \geq 2.5 mg/kg in rats. The main target organ in all species was the skin, irrespective of the application route, with dose-limiting toxicity findings. Further target organs were the bones and the non-glandular stomach or forestomach in rodents, spleen (rodents) and testes (dogs). Minipigs showed no systemic effects, probably due to the low exposure after dermal administration. A NOAEL for male dogs could not be established in the chronic study due to dose-dependent degeneration of germ cells with incomplete recovery and findings in the epididymis. The

NOAEL for female dogs correlates to exposure multiples of 1566. Safety margins in the chronic rat study were 601 (males) and 1877 (females) relative to the maximum recommended human daily dose (MRHD) of 2 g cream (i.e. 100 µg trifarotene). Safety margins could not be established after dermal application, either due to adverse findings in the skin, stomach and bones at the lowest dose level (mice) or undetectable trifarotene levels (minipigs). Overall, effects on bones, skin, spleen and testis are known from other retinoids and are considered of human relevance.

A comprehensive *in vitro* and *in vivo* genotoxicity test battery did not indicate a mutagenic, clastogenic or aneugenic potential of trifarotene.

Two-year carcinogenicity studies in rats (oral) and mice (dermal) did not show any compound-related increase in primary or metastatic neoplastic changes with estimated exposure margins of 23 and 167. Trifarotene had no effect on fertility or mating performance in female and male rats up to the highest oral doses (margins > 1700). In embryo-foetal development studies in pregnant rats and rabbits, trifarotene was embryotoxic (post-implantation losses), teratogenic (multiple external, visceral and skeletal malformations), and caused skeletal variations (e.g. retarded ossification or increased ossification, incomplete rib formation). Exposures at the NOAEL were 534-fold and 98-fold the clinical exposures at the MRHD in rats and rabbits respectively. In a pre- and postnatal development study in rats, no effects on reproductive or clinical parameters were noted. Despite the high safety margins, embryofoetal toxicity is considered a class-related risk requiring contraindication of trifarotene during pregnancy.

A dose range finding study in juvenile dogs did not indicate additional concerns. Acknowledging the known bone and testicular toxicities, a full juvenile study is not considered warranted to support dermal application in children 9 years of age and older.

Trifarotene cream with concentrations > 0.005% is potentially eye-irritating. Different *in vivo* studies showed that trifarotene was a potential skin irritant and photosensitising.

There are no toxicological concerns with regard to impurities or excipients.

A risk to the environment is not expected, and the submitted ERA can be accepted.

Nonclinical Conclusions

The provided data were considered sufficient to perform a risk assessment. There are no major safety issues that would preclude approval of trifarotene in the requested indication as it has a toxicity profile typical of other retinoids. Appropriate recommendations are included in the information for healthcare professionals and the RMP.

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

If at all, very low systemic plasma trifarotene concentrations were observed following repeated doses of the proposed 50 µg/g cream. Overall, it can be assumed that the systemic trifarotene levels are not relevant for the pharmacological effect, and thus the efficacy, of trifarotene.

ADME

The pharmacokinetic profiles of trifarotene in healthy subjects and subjects with acne vulgaris were evaluated in seven clinical studies, two of which can be considered as PK maximal usage trials (MUsT) in patients with acne vulgaris.

Following repeated doses of the proposed 50 µg/g cream in healthy subjects, no quantifiable trifarotene levels were measured after 29 days.

Following daily doses of 2 g of 50 µg/g trifarotene cream under maximal use conditions in subjects with acne vulgaris, 7 of 19 (37%) subjects had measurable trifarotene concentrations, i.e. $C_{max} > 5.0$ pg/mL. Individual peak concentrations ranged up to 9.6 pg/mL, and were reached within approximately 4 h.

The absolute bioavailability was not investigated.

The volume of distribution was not determined.

The analysis of skin samples (tape stripping/punch biopsies) from healthy subjects revealed that trifarotene penetrated the skin to the dermis and epidermis, although trifarotene was mainly detected in the stratum corneum.

It was shown that trifarotene is primarily metabolised via CYP2C9 and, to a lesser extent, via CYP2C8, CYP3A4, and CYP2B6 *in vitro*. Five main metabolites were identified, three of which were shown to be pharmacologically active *in vitro*. Considering the very low systemic exposures, the lack of an *in vivo* ADME study is acceptable. Following the administration of the proposed 50 µg/g cream, none of the four Phase I metabolites were detected in plasma.

Since the very low systemic trifarotene concentrations led to a lack of a distinct elimination phase in the majority of subjects, the half-life could only be determined for three subjects (2.4 h to 9.1 h). Overall, the half-life seems rather short, although an adequate characterisation was not feasible.

Special Populations / Intrinsic Factors

No PK data in subjects with impaired renal or hepatic impairment are available, which is acceptable considering the very low systemic trifarotene concentrations.

No differences in trifarotene exposure were observed between healthy Japanese and non-Japanese subjects.

The exposures in adolescent subjects (12-17 years) with acne vulgaris were comparable with those in adult subjects. This study included only two paediatric patients younger than 12 years (10 and 11 years of age), neither of whom had quantifiable trifarotene plasma concentrations. Furthermore, pharmacokinetic assessments were performed in two subjects (10 and 11 years of age) as part of a long-term safety study, and no trifarotene plasma concentrations were detectable.

Overall, it was not feasible to characterise the PK in 9-11 year old subjects adequately, but it is expected that systemic trifarotene exposures may be generally increased in children. However, considering the low systemic trifarotene levels in adolescents and adults, clinically meaningful differences in children are unlikely.

Interactions

It was shown that trifarotene inhibits CYP2C8 and CYP2C9 *in vitro*. However, considering the low systemic exposures and the determined IC₅₀ values, it is unlikely that trifarotene has an impact on concomitantly administered substrates of CYP2C8 or CYP2C9. Trifarotene did not induce CYP1A2, CYP2B6, or CYP3A4 *in vitro*.

Trifarotene was shown to inhibit the transporters OATP1B1/3, OCT1/2, and BCRP *in vitro*. Again, considering the low systemic exposures to trifarotene, it is unlikely that trifarotene has an impact on concomitantly administered substrates of these transporters.

Although trifarotene was shown to be a substrate of BCRP *in vitro*, this is not considered relevant since the product is a topical cream.

In view of the low systemic trifarotene concentrations up to 9.6 pg/mL, no dedicated drug-drug interaction (DDI) studies are considered necessary because of the *in vitro* findings.

In the context of a DDI study, multiple doses of trifarotene did not have an impact on the PK of the oral contraceptives levonorgestrel and ethinyl estradiol *in vivo*.

Pharmacodynamics

Trifarotene is a potent retinoic acid receptor γ (RAR γ) agonist. No specific clinical PD endpoints were investigated.

Secondary Pharmacology (Safety)

No prolongation of the QTc interval was observed following multiple suprathreshold doses of 12 g of 100 μ g/g trifarotene gel in a vehicle-controlled thorough QT study with moxifloxacin.

6.2 Dose Finding and Dose Recommendation

The main dose finding study (RD.06.SRE.18233) was a multi-centre, randomised, investigator-blind, vehicle- and active-controlled, phase 2 study to assess the efficacy and safety of different concentrations of trifarotene cream in male and female patients aged 12 to 35 years with moderate to severe papulo-pustular facial acne vulgaris.

Five treatments were compared: 25 μ g/g, 50 μ g/g and 100 μ g/g trifarotene cream, 0.1% tazarotene gel as active control and vehicle cream as placebo control, applied as a thin film on the face once daily in the evening for 12 weeks. Concomitant moisturising lotion was used each morning and as desired except within one hour before or after study drug application.

Two co-primary endpoints were evaluated, a qualitative one based on the Investigator's Global Assessment (IGA) of acne severity and a quantitative one based on total acne lesion counts.

From an efficacy point of view, all trifarotene doses were better than the vehicle, but without clear consistent dose-dependency across the two co-primary endpoints. From a safety point of view, the two lower trifarotene concentrations were better tolerated than the highest concentrations. The findings support the choice for the 50 μ g/g trifarotene cream, although the possibility of a better benefit/risk ratio for the 25 μ g/g trifarotene dose strength cannot be ruled out.

6.3 Efficacy

Two identical pivotal phase 3 studies (RD.06.SRE.18251 and RD.03.SRE.18252) with a randomised, vehicle-controlled, double-blind design evaluated the efficacy and safety of the once daily topical application of 50 μ g/g trifarotene cream in male and female paediatric and adult patients with moderate acne vulgaris of the face and trunk over 12 weeks.

Three co-primary efficacy endpoints regarding the facial acne and three identical co-secondary endpoints regarding the truncal acne were defined. They combined qualitative assessments of acne severity using a 5-point scale, as well as quantitative measures of acne severity like non-inflammatory and inflammatory lesion counts.

Further details regarding size, treatments and endpoints are summarised in the information for healthcare professionals in the "Clinical Efficacy" section.

Both pivotal phase 3 studies demonstrated superiority for 50 µg/g trifarotene cream over the vehicle, with statistical significance for all 3 co-primary and all 3 co-secondary efficacy endpoints. Further details of the results are given in the information for healthcare professionals in Tables 3 and 4, “Clinical efficacy” section.

In summary, trifarotene cream (50 µg/g) showed a modest, but consistent treatment effect in patients with moderate acne vulgaris of the face and trunk.

Because no active comparator was included in the studies, the clinical relevance of the modest treatment effect of trifarotene 50 mcg/g cream in both pivotal trials is difficult to judge, especially, as acne vulgaris is a waxing and waning disease, and the natural course of the disease could have played a role. The clinical relevance was also not clear from the subject’s assessment of facial acne improvement (“Supportive Endpoint #5”) and of the “Dermatology Life Quality” (“Other Endpoint #1”). Nevertheless, it is expected that this will provide an additional treatment option for patients who tolerate the treatment well.

6.4 Safety

A total of N=1932 subjects were exposed to trifarotene 50 µg/g cream.

The number of subjects exposed in the two identical pivotal phase 3 studies (RD.06.SRE.18251 and RD.03.SRE.18252) was N=1220, which is the most meaningful Safety Pool for the approved indication and target population in terms of dosage, formulation and dose regimen.

The mean treatment duration was approximately 80 days, while the mean daily medication was 1.5 g of trifarotene cream (50 µg/g).

Among the adverse events (AEs) occurring in at least 1% of the subjects (Safety Pool 1), application site irritation and pruritus, as well as sunburn, were the most frequent and were expected for the class of topical retinoids.

Cutaneous AEs happened with approximately four-fold frequency in trifarotene-treated subjects compared to vehicle-treated subjects.

The most frequent drug-related cutaneous AEs that led to permanent treatment discontinuation were various kinds of administration site conditions (e.g. irritation, dryness, erosion, erythema, and pain) as well as skin disorders (e.g. skin irritation, allergic dermatitis and worsening of acne).

In general, topical retinoids have a known class effect of local skin signs and symptoms such as erythema, scaling, dryness and stinging/burning. These local reactions were systematically collected in the pivotal trials. They increased significantly compared to baseline in the trifarotene treatment groups, with irritation peaking mainly in week 1 for the face, and in weeks 1 to 4 for the trunk.

More details about adverse drug reactions (ADRs) can be found in the information for healthcare professionals in the sections on “Adverse Drug Reactions” and “Local Tolerability”.

The subgroup of patients aged 9 to 11 years in the phase 3 clinical trials was too small to draw any conclusions in terms of safety or efficacy. Consequently, the approved indication is for patients aged 12 and older.

Systemic retinoids are known to be teratogenic. This risk cannot be ruled out for the topical application of trifarotene cream despite low or undetectable plasma concentrations. Consequently, the use of trifarotene cream is contraindicated in case of existing or planned pregnancy.

A phase 3 long-term safety study over 52 weeks (RD.03.SRE.18250) with a single-arm, non-comparative, open-label multicentre design evaluated the safety of once daily 50 µg/g trifarotene cream in male and female patients aged 9 years and older with moderate acne vulgaris on the face and trunk.

N=453 patients were treated in this study; 76.5% completed the study, while 23.5% discontinued prematurely most often due to the subject’s request (11.6%).

This study revealed no evidence of any systemic ADRs. The quality of the local tolerability parameters were as expected for the class of topical retinoids. No new signals were detected.

However, long-term safety beyond one year remains unknown.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Overall, the benefit/risk ratio for 50 µg/g trifarotene cream is considered positive for the treatment of moderate facial and truncal acne vulgaris in patients from the age of 12 years:

A modest but consistent beneficial effect across all co-primary and co-secondary efficacy endpoints was observed in the pivotal studies.

No prohibitive safety signals have been detected. Instead, the frequent expected local cutaneous reactions to topical retinoids occurred, which can easily be recognised and mitigated by precautionary measures such as the frequent use of moisturiser and use of sunscreen with sun protection factor (SPF) >30 prior to sun exposure. Long-term safety beyond 1 year is currently unknown.

The plasma concentrations of 50 µg/g trifarotene cream were either low or not measurable in many patients. Nevertheless, teratogenicity - a known class effect of systemically available retinoids – cannot be ruled out, which is why effective contraceptive measures in females of reproductive age, a contraindication in case of existing or planned pregnancy and a warning against breastfeeding was included in the information for healthcare professionals.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix**8.1 Approved Information for Healthcare Professionals**

Please be aware that the following version of the information for healthcare professionals relating to Aklief, cream was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

AKLIEF® Cream

Composition

Active substances

Trifarotene

Excipients

Purified water, propylene glycol (E1520) 300 mg/g, allantoin, medium-chain triglycerides, phenoxyethanol, cyclomethicone, acrylicamide / sodium acryloyldimethyl taurate copolymer, polysorbate 80, sorbitan monooleate, isohexadecane, ethanol

Pharmaceutical form and active substance quantity per unit

One gram of cream contains 50 micrograms of trifarotene.

Indications/Uses

Aklief is indicated for the topical treatment of moderate* acne vulgaris on the face and/or torso in patients aged 12 and over, if more than half the surface is affected, in the presence of numerous comedones, papules and pustules.

* see section *Properties/Effects*, Table 2

Dosage/Administration

Usual dosage

Aklief cream should be applied once daily in the evenings in a thin layer to clean, dry skin on all areas of the face and/or torso that are affected.

Duration of treatment

The duration of treatment should be determined by the doctor based on the overall clinical condition. Aklief cream was used for no longer than 1 year in clinical trials. Assessment of the continuous improvement by the doctor is recommended after three months of treatment.

Patients with hepatic or renal disorders

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

Elderly patients

The safety and efficacy of Aklief in elderly patients aged 65 and over have not been demonstrated.¹

Children and adolescents

There are insufficient data on the safety and efficacy of Aklief in children aged under 12.

Mode of administration

For cutaneous use only.

Apply a thin layer of Aklief cream once daily in the evenings to clean and dry skin on all areas of the face and/or torso that are affected:

- One actuation of the pump dispenser should be sufficient to apply cream to the face (i.e. forehead, cheeks, nose and chin).
- Two actuations should be sufficient to apply cream to the upper torso (i.e. reachable upper back, shoulders and chest). An additional actuation can be used for the middle and lower back if this is affected by acne.

Patients should be advised to avoid contact with the eyes, lips and mucous membranes and to wash their hands after applying the cream.

Use of a moisturiser is recommended from the start of treatment onwards, allowing for an interval of one (1) hour before and after applying Aklief cream to ensure that the skin has dried.

Contraindications

- Pregnancy (see section *Pregnancy, lactation*)
- Women who are planning a pregnancy
- Hypersensitivity to the active substance or to any of the excipients listed in the section *Composition*.

Warnings and precautions

Erythema, scaling, dryness and stinging/burning may occur when using Aklief cream. The majority of these reactions are mild to moderate and only a few are serious (see section *Undesirable effects*).

Maximum severity typically occurred within the first 4 weeks of treatment and abated over the course of further use of the medicinal product. Patients should be instructed to use a moisturiser from the start of treatment onwards to reduce the risk of such reactions, allowing for an interval of one (1) hour before and after applying Aklief cream. If necessary, Aklief cream can be applied less frequently or the application can be temporarily discontinued. Treatment should be stopped if the serious reactions persist in spite of the measures taken to alleviate them.

Concomitant use of other topical products that are potential irritants (medicinal or abrasive soaps and detergents, soaps and cosmetics with strong skin-drying effects) and products containing high concentrations of alcohol should be avoided as Aklief cream may cause local irritation.

The product should not be applied to cuts, grazes and eczematous or sunburned skin. Hair removal using wax should be avoided on areas of skin treated with Aklief cream, as is the case for other retinoids. Aklief is not suitable for oral, ophthalmological or intravaginal use.

Aklief should not come into contact with the eyes, lips or mucous membranes. If the cream comes into contact with the eyes, they must be rinsed immediately with plenty of warm water.

Excessive exposure to sunlight, including sunlamps and phototherapy, should be kept to a minimum during treatment. Patients should be advised to use a water resistant, broad-spectrum sunscreen with a sun protection factor (SPF) of 30 or higher and to wear protective clothing if exposure to the sun cannot be prevented.

Aklief cream should not be used in women of childbearing age if they are not simultaneously using a reliable contraceptive method (see section *Pregnancy, lactation*). This product contains propylene glycol (E1520), which may cause skin irritation.

Interactions

Effects of Aklief on other medicinal products

A clinical drug interaction study revealed no indications that the topical application of trifarotene has any effect on systemic oral contraceptives (ethinylestradiol and levonorgestrel).

Effects of other medicinal products on Aklief

No clinical drug interactions studies were carried out to investigate the effects of other medicinal products on systemic trifarotene concentrations.

Concomitant topical medicinal products:

Concomitant use of topical medicinal products has not been studied specifically. The following topical products were approved for use in the pivotal studies:

- sunscreen,
- non-comedogenic and hypoallergenic moisturiser (if desired, but observing an interval of approximately 1 hour before and after application of the study medication)
- topical antibiotics prescribed for the treatment of localised pustules (e.g. for selective treatment).

Pregnancy, lactation

Pregnancy

The oral use of retinoids causes congenital malformations. Low systemic exposure is generally assumed due to minimal dermal absorption when topically administered retinoids are used correctly. However, individual factors (e.g. damaged skin barrier, excessive use) may contribute towards increased systemic exposure.

Aklief is contraindicated during pregnancy and in women who are planning a pregnancy (see section *Contraindications*).

Aklief must not be used in women of childbearing age if they are not simultaneously using a reliable contraceptive method.

Animal experiments have revealed reproductive toxicity and teratogenicity following oral administration of trifarotene with high systemic exposure (see section *Preclinical data*).

Treatment must be discontinued if Aklief is used (unintentionally) during pregnancy or if the patient becomes pregnant while using this medicinal product.

Lactation

It is not known whether trifarotene or its metabolites are excreted in breast milk.

Trifarotene was detected in the milk of rats following oral administration.

There are no data on the excretion of topically applied trifarotene into breast milk. A risk to the breastfed child cannot be ruled out and Aklief should therefore not be used during breastfeeding.

Fertility

No fertility studies have been conducted with Aklief in humans.

Testicular toxicity was observed in dogs (see *Preclinical data*).

Effects on ability to drive and use machines

No specific studies have been performed on the effects of Aklief on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are irritation at the administration site, pruritus at the administration site and sunburn. In the overall population in the 12-week pivotal studies, these occurred at an incidence of 2.4% to 6.9% in patients treated with Akliief cream.

Local skin reactions (erythema, scaling, dryness and stinging/burning) may occur when using Akliief cream. These skin reactions are very common (see section *Local tolerability* and *Table 1* below).

List of adverse reactions

The adverse reactions reported in the 12-week vehicle-controlled phase III studies in 1220 patients treated with Akliief (and in whom the frequency for Akliief cream exceeds that for the vehicle cream) are given in the list below.

Adverse reactions are listed below by system organ class and frequency. The frequencies are as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $1 < 100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (frequency cannot be estimated from the available data).

General disorders and administration site conditions

Common: skin irritation, pruritus

Uncommon: pain, dryness, skin discolouration, erosion, rash, swelling

Rare: erythema, urticaria, blisters (vesicles)

Injury, poisoning and procedural complications

Common: sunburn

Skin and subcutaneous tissue disorders

Uncommon: skin irritation, acne, allergic dermatitis, erythema

Rare: asteatotic eczema, seborrheic dermatitis, burning skin, skin fissures, hyperpigmentation of the skin

Eye disorders

Rare: exfoliation (scaling skin) on the eyelid, eyelid oedema

Gastrointestinal disorders

Rare: cheilitis

Vascular disorders

Rare: reddening (flushing)

Local tolerability

In addition to the adverse reactions listed above, local tolerability and symptoms of scaling, dryness, erythema and stinging/burning were documented separately to improve the characterisation of the tolerability profile for Akliief cream (see *Table 1*).

Table 1: Administration site reactions after the start of treatment

	AKLIEF Maximum severity during treatment				Basic cream Maximum severity during treatment			
Face	N=1214 % patients				N=1194 % patients			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Erythema	30.6%	28.4%	6.2%	65.2%	21%	6.8%	0.8%	28.6%
Scaling	37.5%	27.1%	4.9%	69.4%	23.7%	5.9%	0.3%	30.0%
Dryness	39%	29.7%	4.8%	73.4%	29.9%	6.8%	0.8%	37.4%
Stinging/burning	35.6%	20.6%	5.9%	62.1%	15.9%	3.8%	0.5%	20.2%
Torso	N=1202 % patients				N=1185 % patients			
Erythema	26.5%	18.9%	5.2%	50.6%	12.7%	4.4%	0.4%	17.5%
Scaling	29.7%	13.7%	1.7%	45.1%	13.2%	2.6%	0.1%	15.9%
Dryness	32.9%	16.1%	1.8%	50.8%	17.8%	3.9%	0.1%	21.8%
Stinging/burning	26.1%	10.9%	4.3%	41.3%	9.2%	2.2%	0.5%	11.9%

Maximum severity of local reactions occurred on average in Week 1 for the face and in Weeks 2 to 4 for the treatment of the torso, with the symptoms then abating (see *Long-term safety data*).

Long-term safety data

In a one-year open-label safety study involving 453 patients aged 9 and over with acne vulgaris on the face and torso, a total of 18 patients were aged 9 to 11, of whom 13 patients (72.2%) completed the study; 268 patients were aged 12 to 17, of whom 209 patients (78.0%) completed the study; and 169 patients were aged at least 18, of whom 126 patients (74.6%) completed the study.

The pattern of adverse reactions in patients treated with Aklied cream was similar to that in the 12-week vehicle-controlled studies.

Children and adolescents

In clinical phase III studies, 37 children with acne vulgaris aged 9 to 11 were treated with Aklied cream, of whom 18 were treated for up to one year. The safety and efficacy could not be adequately investigated and assessed as patient numbers were low in this age group.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIVIS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Aklief is only intended for once-daily use on the skin.

Excessive use will not achieve more rapid or improved outcomes and pronounced reddening, scaling or skin complaints may occur. In such cases, treatment should be discontinued, a moisturiser should be used and treatment should not be resumed until the skin has recovered.

Treatment

In cases of acute accidental ingestion, appropriate measures should be taken to alleviate symptoms in the event of drowsiness, irritability, abdominal pain, nausea, vomiting, intracranial hypertension. Chronic ingestion of the medicinal product can cause the same adverse reactions as those associated with the excessive intake of vitamin A. Such adverse reactions include blurred vision, bone pain, loss of appetite, dizziness, nausea and vomiting, photosensitivity, dry, itchy or peeling skin, mouth ulcers, alopecia, jaundice, respiratory tract infections, confusion and brittle fingernails.

Properties/Effects

ATC code

Pharmacotherapeutic group: Retinoids for the topical treatment of acne vulgaris.

ATC code: D10AD06

Mechanism of action

Trifarotene is a chemically stable terphenylic acid derivative with retinoid-like activity. It is an effective RAR_{γ} agonist, which is characterised by its high specificity for this receptor in comparison to RAR_{α} and RAR_{β} (50- and 8-fold, respectively, retinoid-X receptor (RXR) activity not included in calculation). Furthermore, trifarotene modulates the retinoid target genes (differentiation and inflammatory processes) in immobilised keratinocytes and reconstructed epidermis.

Pharmacodynamics

Trifarotene exhibited pronounced comedolytic activity in the rhino mouse model, resulting in a reduced comedone count and significantly increased epidermal thickness. Trifarotene exhibited the same comedolytic effect as other known retinoids in this model, at a dose that was around 10 times lower.

Trifarotene also exhibited anti-inflammatory and depigmentation effects.

Clinical efficacy

Aklief cream, applied once daily in the evenings, was evaluated over 12 weeks in 2 randomised, multi-centre, double-blind, vehicle-controlled, parallel-group studies with the same design. A total of

2420 patients aged at least 9 with moderate acne vulgaris on the face and torso (the latter was optional for children aged between 9 and 11) were included in the studies.

The severity of acne was assessed separately for each anatomical area on a 5-point scale, on the face (Investigator's Global Assessment, IGA) and torso (Physician's Global Assessment, PGA), with the acne being defined as "moderate" with a score of "grade 3 moderate" (see Table 2).

Table 2. Acne severity scale based on the overall assessment by the physician (IGA and PGA)

0	No manifestation	Clear skin without inflammatory or non-inflammatory lesions
1	Almost no manifestation	A few scattered comedones and a few small papules
2	Mild	Easy to recognise: less than half the face is affected. Some comedones and some papules and pustules.
3	Moderate	Over half the surface is affected. Numerous comedones, papules and pustules. A nodule may be present.
4	Severe	The entire surface is affected. Covered with comedones, numerous papules and pustules. A few nodules may be present.

There were three co-primary and three identical co-secondary study endpoints for efficacy on the face and torso in the two pivotal studies: 1) The rate of success based on the overall assessment by the physician (IGA and PGA), defined as the percentage of study participants with skin with "no manifestation" or "almost no manifestation" (grade 0 or 1) and an improvement by at least 2 grades at Week 12 in comparison to baseline, as well as absolute changes at Week 12 in comparison to baseline in 2) inflammatory lesions (papules and pustules) and 3) non-inflammatory lesions (comedones).

Overall, 87% of patients were white and 55% were female. 34 (1.4%) patients were aged 9 to 11, 1128 (47%) subjects were aged 12 to 17, and 1258 (52%) subjects were aged at least 18. All patients had moderate acne vulgaris on the face and 99% on the torso. At the beginning of the study, subjects had between 7 and 200 (mean: 36) inflammatory lesions on the face and between 0 and 220 (mean: 38) on the torso. In addition, the patients had between 21 and 305 (mean: 52) non-inflammatory lesions on the face and between 0 and 260 (mean: 46) on the torso.

The IGA and PGA rates of success and the mean absolute reduction in the acne lesion counts compared to baseline after 12 weeks of treatment are given in the tables below:

Table 3: Improvement in facial acne based on Investigator's Global Assessment (IGA) and changes in lesion count at Week 12 (intention-to-treat; multiple imputation)

	Study 1		Study 2	
	Aklief cream	Vehicle cream	Aklief cream	Vehicle cream
	N= 612	N= 596	N= 602	N= 610

Rate of success based on IGA, (% patients) Improvement by at least 2 grades and IGA of “no manifestation” (0) or “almost no manifestation” (1)	29.4a	19.5	42.3a	25.7
Inflammatory lesions (Number of lesions) Mean absolute change compared to baseline	-19.0a	-15.4	-24.2a	-18.7
Non-inflammatory lesions (Number of lesions) Mean absolute change compared to baseline	-25.0a	-17.9	-30.1a	-21.6

a) $p < 0.001$ vs vehicle

Table 4: Improvement in acne on the torso based on Physician's Global Assessment (PGA) and changes in lesion count at Week 12 (intention-to-treat; multiple imputation)

	Study 1		Study 2	
	Aklief cream	Vehicle cream	Aklief cream	Vehicle cream
	N= 600	N= 585	N= 598	N= 609
Rate of success based on PGA, (%) (% patients) Improvement by at least 2 grades and PGA of “no manifestation” (0) or “almost no manifestation” (1)	35.7a	25.0	42.6a	29.9
Inflammatory lesions (Number of lesions) Mean absolute change compared to baseline	-21.4a	-18.8	-25.5a	-19.8
Non-inflammatory lesions (Number of lesions) Mean absolute change compared to baseline	-21.9a	-17.8	-25.9a	-20.8

a) $p < 0.001$ vs vehicle

Pharmacokinetics

Absorption

Absorption of trifarotene from Akliel cream was investigated for maximal usage (Maximal Usage Trial, MUsT) in two clinical studies on the pharmacokinetics, in which 19 adults and 17 children (aged 10-17) with acne vulgaris participated. For 30 days, 2 grams of Akliel daily were applied to the face, shoulders, chest and upper back. After 4 weeks of treatment, 7 of the 19 (37%) adult subjects exhibited quantifiable plasma trifarotene concentrations. C_{max} ranged between a value below the limit of quantification (LOQ <5 pg/ml) and 10 pg/ml, and AUC_{0-24h} ranged between 75 and 104 pg*hr/ml. Three of the 17 (18%) paediatric patients exhibited quantifiable systemic exposure. C_{max} ranged between a value below the limit of quantification (LOQ <5 pg/ml) and 9 pg/ml, and AUC_{0-24h} ranged between 89 and 106 pg*hr/ml.

Steady state was reached in the adult and paediatric patients after 2 weeks of topical application. No drug accumulation is to be expected for 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 revealed that over 99.9% of trifarotene is bound to plasma proteins. No significant binding of trifarotene to erythrocytes was observed.

Metabolism

In-vitro studies conducted with human liver microsomes and recombinant CYP450 enzymes have revealed that trifarotene is primarily metabolised by CYP2C9, CYP3A4, CYP2C8 and, to a lesser extent by CYP2B6.

Potential for drug interactions

In-vitro studies show that Akliel cream does not inhibit the CYP450 isoenzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 at therapeutic concentrations and does not induce CYP1A2, 2B6 or 3A4.

In-vitro studies have revealed that Akliel cream inhibits neither the MATE, OATP, OAT or OCT uptake transporters at therapeutic concentrations, nor the BCRP, PgP, BSEP or MPR efflux transporters.

Elimination

Not applicable.

Preclinical data

Please note: The multiples for comparing systemic exposure in animals with that in humans are based on comparisons of the AUC (Area Under the Curve) for a topical daily dose of 2 g Akliel cream in humans.

Preclinical data from conventional studies on safety pharmacology, toxicity after repeat oral administration, genotoxicity, phototoxicity or on carcinogenic potential indicate no specific risks to humans.

The systemic exposure to trifarotene was very low, generally below the limit of quantification, in studies conducted on dermal toxicity after repeat doses given to minipigs over a maximum of 9 months. There were no systemic effects and the only notable finding was that of reversible skin irritation at the administration sites.

Minimal to mild effects were noted on the stomach and bones in dermatological studies carried out on mice, most likely due to ingestion through licking.

These findings are known effects of retinoids and were confirmed in systemic studies conducted on rats and dogs.

After oral administration to rats and dogs, trifarotene caused toxicity typical of retinoids, affecting the skin, spleen, bones, stomach and testicles, in at least one species.

No adverse effects were observed (NOAEL) in rats, at 0.5 mg/kg/day in males and 0.2 mg/kg/day in females, corresponding to a safety margin of at least 601 when compared with maximum exposure in humans.

Germ cell degeneration, with pyknotic / apoptotic germ cells, was already observed after oral administration to dogs at the lowest dose of 0.02 mg/kg/day. Hypospermatogenesis and deposits in the epididymis were also observed in all animals with this finding. These effects had not abated after 8 weeks, pointing to a significantly more comprehensive and potentially chronic effect.

Exposure at this dose was at least 1170 times higher than the maximum exposure in patients.

However, trifarotene administered orally to rats had no negative effects on fertility at exposures that were approximately 1754-fold (males) and 1877-fold (females) the human exposure at a 2 g dose.

A teratogenic and embryotoxic effect was determined during organogenesis when trifarotene was administered orally to gravid rats and rabbits in animal experiments conducted in reproductive studies. Systemic exposures (AUC) in these experiments corresponded to 1614-fold and 800-fold the human exposure in rats and rabbits, respectively.

Trifarotene had no teratogenic effects at systemic exposures in rats and rabbits equating to 534-fold and 98-fold the human exposure, respectively.

In rats, trifarotene had no effects on pre- and postnatal development at the highest tested oral dose with related systemic exposures (AUC) 595-fold the human exposure.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Shelf life after opening: 6 months

Special precautions for storage

Store at room temperature (15-25 °C).

Keep out of the reach of children.

Authorisation number

67632 (Swissmedic)

Packs

30 g or 75 g pump dispenser (B).

Marketing authorisation holder

Galderma SA, 6330 Cham

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