New Medicine Assessment

Trifarotene (Aklief®) 50 microgram/g cream

Indication under review: 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.

Recommendation: Green

Appropriate for initiation and ongoing prescribing in both primary and secondary care.

Generally, little or no routine drug monitoring is required.

Summary of supporting evidence:

Trifarotene provides an additional treatment choice for moderate acne vulgaris in the therapeutic class of topical retinoids.

Trifarotene is a novel fourth-generation locally applied retinoid approved in the regimens of both face and truncal acnes. Trifarotene, adheres precisely to RAR-gamma, the epidermis' most frequent isoform.

Aklief cream applied once daily in the evening was evaluated for 12 weeks in 2 randomized, multi-centre, parallel group, double-blind, vehicle-controlled studies of identical design (PERFECT Trials). 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.

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. All primary efficacy endpoints were met.

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

Details of Review

Name of medicine (generic & brand name) Trifarotene (Aklief®)[1]
Strength(s) and form(s): 50 microgram/g cream. Supplied as 75g multidose container with airless pump
Dose and administration: 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. There is approximately 0.5 g per actuation of the pump and approximately 150 actuations in a 75g pump.[2]
BNF therapeutic class / mode of action: Skin / Acne
Licensed indication(s): 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.[1]
Proposed use (if different from, or in addition to, licensed indication above): N/A
Course and cost: £27.75 for 75g[3] (treatment assessed after 3 months for efficacy) One pump actuation (0.5g) should be enough to cover the face (i.e. forehead, cheeks, nose, and chin). Two pump actuations (1g) should be enough to cover the upper trunk (i.e. reachable upper back, shoulders and chest). One additional pump actuation (0.5g) may be used for middle and lower back if acne is present. After first opening: use within 6 months. If patient was to apply recommended amount to all three areas mentioned above simultaneously ie 2g in total, then one 75g container should last approximately 1 month ie 37 days. If a patient was using solely on their face then one container should last approximately 5 months.
Current standard of care/comparator therapies: • Retinoid and related drugs • NICE NG198[4] recommends to offer people with acne a 12-week course of 1 of the following first-line treatment options, taking account of the severity of their acne and the person's preferences, and after a discussion of the advantages and disadvantages of each option ○ a fixed combination of topical adapalene with topical benzoyl peroxide for any acne severity ○ a fixed combination of topical tretinoin with topical clindamycin for any acne severity ○ a fixed combination of topical benzoyl peroxide with topical clindamycin for mild to moderate acne ○ a fixed combination of topical adapalene with topical benzoyl peroxide, together with either oral lymecycline or oral doxycycline for moderate to severe acne ○ topical azelaic acid with either oral lymecycline or oral doxycycline for moderate to severe acne.
Relevant NICE guidance: Acne vulgaris: management NICE guideline [NG198] Published: 25 June 2021 SMC2441[5] - Trifarotene (Aklief®) is accepted for use within NHSScotland.

Background and context

SMC2441 - Trifarotene (Aklief®) was discussed at the October 2022 LSCMMG meeting and was prioritised for review.

Trifarotene provides an additional treatment choice for moderate acne vulgaris in the therapeutic class of topical retinoids.

Trifarotene is a novel fourth-generation locally applied retinoid approved in the regimens of both face and truncal acnes. Trifarotene,adheres precisely to RAR-gamma, the epidermis' most frequent isoform.

Acne is a common inflammatory skin condition[6] that leads to lesions which consist of non-inflammatory comedones, and inflammatory papules, pustules, nodules and cysts. In patients with acne, lesions and/or scarring may be seen and severity can range from mild lesions to permanent disfiguration. It can also have a psychological and social impact on the patient.

Acne vulgaris is a common type of acne that primarily affects the face, back, and chest; it is most common in adolescence, but may affect those in any age group.

The severity of acne varies along a continuum from mild to moderate to severe, that is characterised by the lesion type(s) and quantity. Patients with mild to moderate acne are those with 1 or more of the following: non-inflammatory lesions (of any number), up to 34 inflammatory lesions, up to 2 nodules. Patients with moderate to severe acne are those who have 35 or more inflammatory lesions and/or 3 or more nodules.

Treatment aims to reduce the severity of skin lesions and other complications, and to prevent recurrence and scarring.

Summary of evidence

Summary of efficacy data in proposed use [1]:

Aklief cream applied once daily in the evening was evaluated for 12 weeks in 2 randomized, multi-centre, parallel group, double-blind, vehicle-controlled studies of identical design (PERFECT Trials) [7]. 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).

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:

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
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

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*	-
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

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:

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*	-

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*	-
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.

Summary of safety data [1]:

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.

Summary of safety profile

Local cutaneous reactions such as erythema, scaling, dryness, and stinging/burning) were collected separately from other adverse events as a measure of local tolerance. These cutaneous reactions are very common and of mild, moderate and severe intensity for up to 39%, 29.7% and 6.2% of patients, respectively on the face. On the trunk, up to 32.9%, 18.9%, 5.2% of patients had mild, moderate and severe reactions respectively. The maximum severity typically occurred at Week 1 for the face, and at Week 2 to 4 for the trunk, and decreased with continued use of the medication

The most “commonly” reported adverse reactions as described below in Table 1 are application site irritation, application site pruritus and sunburn, occurring in 1.2% to 6.5% of patients treated with 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 below.

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).

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 Skin fissures Skin hyperpigmentation
Eye disorders	Rare	Eyelid exfolliation Eyelid oedema
Gastrointestinal disorders	Rare	Cheilitis
Vascular disorders	Rare	Flushing

Contraindications: Pregnancy, Women planning a pregnancy, Hypersensitivity to the active substance or to any of the excipients
Special Warning: 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.

Strengths and limitations of the evidence:

Strengths

- Two randomized, multi-centre, parallel group, double-blind, vehicle-controlled studies of identical design with 2420 patients
- Primary and secondary endpoints were all met with statistical significance.
- 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.

Limitations

- The two randomized, multi-centre, parallel group, double-blind studies were vehicle controlled, no comparator product used.
- Duration of trials (other than safety trial) was only 12 weeks

Summary of evidence on cost effectiveness:

NHS List Prices March 2023 [3]

Trifarotene 75g = £27.75 (equivalent to £0.37 / g)

Adapalene 0.1% / Benzoyl peroxide 2.5% gel 45g = £19.53 (£0.43 /g)

Adapalene 0.3% / Benzoyl peroxide 2.5% gel 45g = £19.53 (£0.43 / g)

Clindamycin 1% / Tretinoin 0.025% gel 30g = £11.94 (£0.40 / g)

Benzoyl peroxide 3% / Clindamycin 1% gel 30g = £13.14 (£0.44 / g)

Benzoyl peroxide 5% / Clindamycin 1% gel 30g = £8.92 (£0.30/g)

Trifarotene (Aklief) is of a comparable cost to the other currently available, NICE recommended topical acne therapies.

Prescribing and risk management issues:

These would be identical to those for the other retinoid medications already prescribed.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
Trifarotene provides an additional treatment choice for moderate acne vulgaris in the therapeutic class of topical retinoids.
Financial implications of the intervention:
None
Service Impact Issues Identified:
No service impact is expected as this product would be available as an alternative treatment option.
Equality and Inclusion Issues Identified:
None anticipated.
Cross Border Issues Identified:
Pan Mersey[8] - currently have Trifarotene (Aklief) as GREY ie Not recommended for use at this time. Deviation from the policy may be considered on an individual basis where exceptional circumstances exist. This recommendation will be reviewed if a formal application for use is received and prioritised for in-year review. GMMMG[9] – currently have Trifarotene (Aklief) out for consultation (consultations close 30.3.23) with the recommendation of a GREEN RAG Rating.
Legal Issues Identified:
None identified.
Media/ Public Interest:

N/A

References

[1] SPC Trifarotene (Aklief) 50 microgram/g cream https://www.medicines.org.uk/emc/product/13881/smpc#

[2] Information obtained from Medical Information at Galderma

[3] NHS Electronic Drug Tariff March 2023 https://www.drugtariff.nhsbsa.nhs.uk/#/00835481-DD_1/DD00834969/Part%20VIIIA%20products%20T

[4] Acne vulgaris: management NICE guideline [NG198]Published: 25 June 2021 https://www.nice.org.uk/guidance/ng198/chapter/Recommendations

[5] SMC2441 trifarotene (Aklief) https://www.scottishmedicines.org.uk/medicines-advice/trifarotene-aklief-abb-smc2441/

[6] BNF Acne https://bnf.nice.org.uk/treatment-summaries/acne/

[7] Tan J., Thiboutot D., Popp G., et al. Randomized phase 3 evaluation of trifarotene 50 μg/g cream treatment of moderate facial and truncal acne. Journal of the American Academy of Dermatology . 2019;80(6):1691–1699. https://pubmed.ncbi.nlm.nih.gov/30802558/

[8] Pan Mersey APC Formulary https://formulary.panmerseyapc.nhs.uk/chaptersSubDetails.asp?FormularySectionID=13&SubSectionRef=13.06.01&SubSectionID=D100#5827

[9] GMMMG Consultations https://gmmmg.nhs.uk/consultation-actions-from-february-2023-meeting-of-crg/