AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report – Limited submission

Trifarotene (Aklief®▼) 50 microgram/g cream

Company: Galderma (UK) Ltd

Licensed indication under consideration: 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

▼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 adverse reactions.

Marketing authorisation date: 13 January 2020

Comparator(s)

- Adapalene (Differin 0.1% w/w cream®). The company does not consider adapalene (Differin 0.1% w/w gel®) as a comparator treatment as this is usually prescribed for oily skin where cream is for those with dry skin.

Limited submission details

- Trifarotene for the above indication meets the All Wales Medicines Strategy Group (AWMSG) criteria to be appraised as a full submission as it is a new licensed medicine. However, the criteria for appraisal are currently being reviewed.
- The applicant company justify their limited submission as this is a fourth-generation retinoid with low eligible population estimates and price parity with the comparator medicine.
- All Wales Therapeutics and Toxicology Centre (AWTTC) acknowledge trifarotene is an additional treatment option within an existing therapeutic class and anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

Clinical effectiveness

- *Acne Vulgaris* is a chronic inflammatory disease and topical retinoids are recommended for the treatment of acne since they affect multiple aspects of acne pathophysiology.

- Trifarotene is a novel fourth-generation topical retinoid that adheres specifically to retinoid acid receptor (RAR)-gamma, the epidermis' most frequent isoform.
- NICE Guideline (NG) 198 for the treatment of *Acne Vulgaris* recommends five first line treatment options. These include four topical fixed-dose combination treatments (adapalene/benzoyl peroxide, tretinoin/clindamycin, benzoyl peroxide/clindamycin and adapalene/benzoyl peroxide plus oral lymecycline or doxycycline) and topical azelaic acid with either oral lymecycline or doxycycline depending on a person's preferences and disease severity. Monotherapy treatment with benzoyl peroxide is recommended as an alternative option if any fixed-dose combination therapies are contraindicated, or a person wishes to avoid using a topical retinoid or topical/oral antibiotic.
- The company anticipate place of therapy for trifarotene as an alternative to other available retinoids in patients with moderate facial and/or truncal acne when a topical retinoid monotherapy is thought clinically appropriate or preferred by patients who may have contraindications, or who do not wish to use fixed-dose combination options, or products containing an antibiotic. Due to no clinical data surrounding the concomitant use of trifarotene and benzoyl peroxide, the applicant company is not proposing use of trifarotene in combination with benzoyl peroxide.
- Welsh local clinical guidelines for dermatology in primary care are broadly in line with NG198 and Welsh clinical experts welcome a new therapeutic treatment option.
- The company propose adapalene 0.1% (Differin®) as the comparator treatment as it is specifically indicated for the treatment of mild to moderate acne; trifarotene studies included people with moderate acne. The company highlight that the fixed-dose combination treatments are not considered relevant comparators to trifarotene as they are not expected to be displaced in Welsh clinical practice by a topical retinoid monotherapy. Welsh expert opinion sought by AWTTC agree with the company's choice of comparator and that the retinoid fixed-dose combinations with benzoyl peroxide or antibiotics are not suitable comparator treatments.
- Welsh prescribing usage data for October 2022 to September 2023 obtained by AWTTC shows adapalene (includes Differin® 0.1%) accounts for 10.3% proportion cost for all topical preparations prescribed for acne. Benzoyl peroxide monotherapy accounts for 4.9% and adapalene plus benzoyl peroxide (includes Epiduo®) fixed-dose combination treatment accounts for 19.6%. The company suggests that benzoyl peroxide monotherapy is not considered a relevant comparator treatment as it is not in the same therapeutic class as trifarotene and is usually recommended for mild acne.
- The company submission includes results from two phase III multicentre randomised, double-blind, controlled 12-week studies (PERFECT 1 and PERFECT 2) that compared doses of once-daily 50 mcg/g trifarotene versus placebo. Children aged nine years of age or older with moderate acne of the face (defined as Investigators Global Assessment (IGA) score of 3, ≥ 20 inflammatory lesions and ≥ 25 non-inflammatory lesions) and trunk (defined as Physician Global Assessment (PGA) score of 3,

≥ 20 inflammatory lesions (IL) and 20 to < 100 non-inflammatory (NIL) lesions on the areas of the trunk reachable for self-application) were included. A total of 2420 patients across both studies were randomised with 1214 patients receiving trifarotene and 1206 patients receiving placebo.

- The primary endpoints were rate of success on the face, as determined by the Investigator's Global Assessment (clear or almost clear and ≥ 2 grade improvement), and absolute change from baseline in inflammatory and non-inflammatory counts from baseline to week 12.
- Secondary endpoints included rate of success, as determined according to the PGA (defined as percentage of patients achieving a rating of clear or almost clear on and at least a 2-grade change from baseline) at week 12; absolute change in truncal inflammatory lesion count from baseline to week 12; and absolute change in truncal non-inflammatory lesion count from baseline to week 12.
- The results of all co-primary and co-secondary efficacy assessments in both studies at week 12 were statistically significant ($P < 0.001$) in favour of trifarotene versus placebo.
- Safety data from the phase III study described above did not identify any new safety concerns. Local irritation related to trifarotene cream was transient and consistent with the known pattern of topical retinoid dermatitis. Severe adverse events (SAE) considered related to trifarotene therapy were reported in nine patients (PERFECT 1 and 2 combined) and included skin irritation, sunburn, dermatitis allergic, application site pain, erosion, and irritation vs none in the placebo group. AEs led to discontinuation in 1.9% (PERFECT 1) and 1.2% (PERFECT 2) of the trifarotene group and in no patients in the placebo group.
- The one-year open label extension to the PERFECT studies (the Satisfy study) demonstrated a clinically meaningful improvement over time and longer-term safety with IGA and PGA success rates increasing from 22% at week 12 to 57.9% at Week 52.
- In the absence of direct comparative efficacy data comparing trifarotene with adapalene 0.1% a literature review was conducted which identified a frequentist network meta-analysis (NMA) comparing the effectiveness of a range of most commonly prescribed topical therapies licensed for the treatment of mild to moderate acne in the UK but did not include trifarotene as it was not available at the time of the study. Due to heterogeneity in patient populations and variable reporting outcomes in clinical trial publications and as many studies pre-dated 2009 an NMA of published data would have limitations to enable a robust comparison of the efficacy and safety of trifarotene versus adapalene 0.1% (Differin®).
- The company submission therefore included comparative efficacy data through an indirect treatment comparison (ITC). The ITC takes the form of a relative effectiveness assessment (REA) using individual patient data (IPD) for patients with moderate acne from the pivotal trials for trifarotene (PERFECT 1 and 2 studies) and for the comparator adapalene 0.1% from two randomised controlled studies of Epiduo® 0.1% which include an adapalene treatment arm (studies 18087 and 18088).
- Efficacy endpoints comparing trifarotene to adapalene 0.1% in patients aged ≥ 12 years with moderate acne of the face at week 12 include percentage of patients who achieve IGA scores 0 or 1 (with at least a

2-grade change from baseline) (defined as an “IGA success”); mean and percentage change in inflammatory lesion count of the face from baseline; mean and percentage change in non-inflammatory lesion count of the face from baseline. The PERFECT studies included secondary endpoints relating to truncal acne. Due to the lack of truncal acne outcomes for the adapalene 0.1% studies it was not possible to compare truncal outcomes. The company highlight the results for the face can be generalised to the trunk. The base case results of the REA demonstrated that trifarotene versus adapalene 0.1% was found to have better outcomes for moderate facial acne at 12 weeks across all of the key efficacy endpoints.

- The company contacted an acne clinical study disease expert who advised that it was important that patient populations compared across trials were similar in terms of their prognostic outlook at baseline. One prognostic factor the expert thought could bias the facial acne outcomes, if not matched, was the existence of acne of the trunk. As a result, in the adapalene 0.1% studies, 45% of patients in each arm were excluded from the ITC despite having facial acne outcomes due to a lack of information about trunk acne. The company acknowledge the limitations with this approach.
- The number of patients that experienced a treatment related SAE were low across both the trifarotene and adapalene 0.1% studies at 0.46% (6/1308). For the comparison of SAEs there is a numerical difference in favour of trifarotene, however this is not statistically significant, and with such low numbers of observations there appears to be a low risk of SAEs with either treatment.
- A limitation of the company submission is a lack of direct comparative data and no indirect comparison to any of the other possible treatment options with the exception of adapalene 0.1%.
- The applicant company describe an advantage of trifarotene as a metered pump dispenser which will be more convenient for the patient and less wastage. The comparator medicine is available in a tube where each dose is squeezed directly from the tube.
- The Medicines and Healthcare products Regulatory Agency (MHRA) advises that systemic exposure is thought to be negligible following application of topical retinoids. However, since risk cannot be excluded, use of topical retinoids is contraindicated during pregnancy as a precaution; the MHRA advises females of childbearing potential should use effective contraception.
- Trifarotene is accepted for use in NHS Scotland following an abbreviated submission to Scottish Medicines Consortium and is available by local decision in NHS England.

Budget impact

- The company estimate 45,587 people in Wales have moderate acne. This estimate is based on Office for National Statistics Wales population estimates, English prevalence rates from Kuan et al 2019 for all grades of acne (mild, moderate and severe) and an estimate that 20% have moderate acne based on prevalence rates published in the NICE knowledge summary. Welsh prescribing data suggests approximately 19%

receive NHS prescriptions for topical acne treatment and of these 10.3% (889 patients) currently receive single agent adapalene 0.1% (Differin®).
- Trifarotene is estimated to replace a proportion of single agent adapalene, no other existing medicines are displaced. The budget impact analysis assumes that in a market with trifarotene 220 patients in Year 1 increasing to 440 in Year 3 will receive trifarotene, based on a market share of 25% in Year 1 and 50% in Year 3 (and allowing for a 1% discontinuation rate). The number of patients estimated to receive trifarotene in years 4 and 5 remains stable as 440. Costs in the base case analysis are calculated assuming that both face and truncal acne use three actuations per day (1.5 mg) with one actuation estimated for the face and two for the trunk. The daily dose of adapalene 0.1% (Differin®) is assumed the same as trifarotene as per Summary of Product Characteristics (SmPC).
- This results in a net medicine budget impact of £0 in all of Years 1 to 5 on the basis that adapalene 0.1% (Differin®) will only be expected to be displaced in clinical practice with a same cost per gram as trifarotene.
- Whilst the company estimate minimal budget impact this is based on one comparator and monotherapy only. NG198 recommend a number of first-line combination treatment options.

Additional information

- AWTTC is of the opinion that, if recommended, trifarotene (Aklief®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

Evidence search

Date of evidence search: 14 December 2023, 1 February 2024.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Trifarotene (Aklief®▼) 50 microgram/g cream Reference number: 3153. February 2024.