

Resubmission

adapalene 0.1%/benzoyl peroxide 2.5% gel (Epiduo®) SMC No. (682/11)

Galderma UK Ltd

07 March 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission:

adapalene 0.1%/benzoyl peroxide 2.5% gel (Epiduo®) is accepted for restricted use within NHS Scotland.

Indication under review: cutaneous treatment of acne vulgaris when comedones, papules and pustules are present.

SMC restriction: the treatment of mild to moderate facial acne when monotherapy with benzoyl peroxide or adapalene is not considered appropriate.

In 12-week studies, adapalene 0.1%/benzoyl peroxide 2.5% gel was as effective as an alternative combination antibiotic treatment in reducing inflammatory lesions. However adapalene 0.1%/benzoyl peroxide 2.5% gel was less well tolerated in terms of local reactions.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of adapalene 0.1%/benzoyl peroxide 2.5% gel. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Cutaneous treatment of acne vulgaris when comedones, papules and pustules are present.

Dosing Information

The gel should be applied to the entire acne affected area once a day in the evening on a clean and dry skin. A thin film of gel should be applied, with the fingertips, avoiding the eyes and lips. The treatment duration should be determined by the doctor on the basis of the clinical condition. Early signs of clinical improvement usually appear after 1 to 4 weeks of treatment. The safety and effectiveness of Epiduo[®] have not been studied in children below 9 years of age.

Product availability date

January 2010

Summary of evidence on comparative efficacy

Acne is the most common skin condition affecting young people. Adapalene is a topical retinoid-like agent used to treat mild to moderate acne. Benzoyl peroxide is commonly used in mild to moderate acne and has antimicrobial, exfoliative and keratolytic properties. Epiduo[®] gel is a once daily, fixed-dose combination preparation containing adapalene 0.1% and benzoyl peroxide 2.5% gel with anti-comedogenic, comedolytic, anti-inflammatory and bactericidal properties.¹

Epiduo[®] gel has a marketing authorisation for the cutaneous treatment of acne vulgaris when comedones, papules and pustules are present. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product when positioned for the treatment of mild to moderate facial acne, when inflammatory lesions (papules and pustules) are present. The submitting company suggests that the appropriate positioning for Epiduo[®] in clinical practice is when monotherapy with benzoyl peroxide or adapalene is not considered appropriate.

There are comparative efficacy data from two randomized, investigator-blind, 12-week studies comparing Epiduo[®] with Duac[®] (clindamycin 1%/benzoyl peroxide 5% gel). One study has been published but the other has not.^{2,3}

In the published study, 382 patients aged 12 to 45 years with mild to moderate facial acne (25 to 80 inflammatory lesions [including the nose], 12 to 100 non-inflammatory lesions [excluding the nose] and no facial nodular cystic lesions) were randomised equally to receive Epiduo[®] or Duac[®] applied once daily in the evening.² The primary outcome was the percentage change in inflammatory lesions (papules and pustules, including nasal lesions) from baseline to week 12. There was a 72% reduction in inflammatory lesions in the Epiduo[®] group compared with a 77% reduction in the Duac[®] group: the difference between groups was not statistically significant ($p=0.076$).²

Key secondary outcomes included the proportion of patients achieving treatment success (defined as an improvement of ≥ 2 grades from baseline to week 12 in the investigator's static

global assessment [ISGA]), which was significantly higher in the Duac[®] than Epiduo[®] group (31% [58/190] versus 22% [42/192] respectively, p=0.046). The time to treatment success from baseline was significantly shorter in the Duac[®] group compared with the Epiduo[®] group (p=0.035), although further details were not reported. There was no significant difference in the percentage change in total lesion count from baseline to week 12: 69% and 67% in the Duac[®] and Epiduo[®] groups respectively.²

Supportive data come from a pooled analysis of three similar, randomised, double-blind, 12-week studies in which 3,855 patients with mainly moderate acne were randomised to receive Epiduo[®], adapalene, benzoyl peroxide or vehicle gel (placebo).⁴ The primary efficacy outcome was success rate defined as the proportion of patients rated as clear or almost clear at week 12 based on the investigator's global assessment. At week 12, success was achieved by 33% of Epiduo[®], 23% of benzoyl peroxide, 20% of adapalene and 14% of vehicle patients; significantly greater in the Epiduo[®] than monotherapy or vehicle groups. Since the net beneficial effect (active – vehicle) of Epiduo[®] was greater than the sum of the net beneficial effects of the individual components, a synergistic effect was concluded.

An open-label, single-arm, 12-month study in 452 patients with moderate acne found that the initial reduction in lesion counts achieved with Epiduo[®] applied once daily was maintained for one year.⁵

A randomised, double-blind, 12-week study in 285 patients, aged 9 to 11 years with moderate acne compared Epiduo[®] with vehicle gel.⁶ The primary outcome was success rate, defined as the proportions of patients rated as clear or almost clear with at least a two grade reduction from baseline in the total lesion count at week 12 and this was achieved in significantly more Epiduo[®] than vehicle patients: 49% versus 16% (p<0.0001).

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the published comparative study with Duac[®], described above, treatment-related adverse events were reported in 79% (151/192) Epiduo[®] patients and 48% (92/190) Duac[®] patients, mainly in the form of mild to moderate application site reactions.² However, severe adverse events were reported in 21% (41/192) and 7.4% (14/190) of patients respectively. There was a significantly higher incidence of local reactions in the Epiduo[®] group compared with the Duac[®] group (p<0.03). Duac[®] was significantly better tolerated at all grades than Epiduo[®] from weeks 1 to 12 in terms of erythema, dryness and peeling as rated by the investigator and of pruritus, burning and stinging as rated by the patient (p<0.05). During the first 2 to 4 weeks of study treatment, Epiduo[®] treated patients experienced significantly more grade 2 to 3 reactions (p<0.05). Study withdrawal due to adverse events was reported in 4.7% (9/192) Epiduo[®] and 1.6% (3/190) Duac[®] patients.²

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The treatment of acne is generally determined by the severity and extent of the condition. Mild and moderate acne is generally treated with topical agents including benzoyl peroxide, retinoids and antibiotics either alone or in combination. In moderate acne, oral treatment with antibiotics or antiandrogens may also be needed.

The submitting company has requested that the SMC considers the use of Epiduo[®] when positioned for use for the treatment of mild to moderate facial acne, when inflammatory lesions (papules and pustules) are present (which is defined in the company submission as “mild to moderate inflammatory acne”). The submitting company suggests that the appropriate positioning for Epiduo[®] in clinical practice is when monotherapy with benzoyl peroxide or with adapalene (the individual components of Epiduo[®]) is not considered appropriate.

There are two 12-week studies versus Duac[®] which is a relevant comparator in Scottish practice. One study has been published but the other has not.^{2,3} The available comparative data found no significant difference between Epiduo[®] and Duac[®] over the 12-week study periods when assessed by the primary outcomes: the percentage change in inflammatory lesions from baseline to week 12. However some secondary outcomes found that Duac[®] was more effective than Epiduo[®]: the proportion of patients achieving treatment success and time to treatment success significantly favoured Duac[®] in the published study.² Duac[®] appeared to be better tolerated in both studies with lower incidences of dermatological adverse events.^{2,3} There are no comparative data for Epiduo[®] versus Zineryt[®] which is also in common use in Scottish practice. However recent European guidelines do not recommend its use for the treatment of mild to moderate papulopustular acne.⁸

The introduction of Epiduo[®] would offer a further fixed-dose topical combination preparation for patients with mild to moderate acne. This is the only available combination of a topical retinoid and benzoyl peroxide and provides an alternative which may reduce the use of topical antibiotics. Unlike Duac[®], its duration of treatment is not limited to 12 weeks. It is also licensed for use in patients >9 years old (Duac[®] is for patients >12 years).^{1,9}

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing Epiduo[®] and Duac[®] for the cutaneous treatment of mild to moderate acne vulgaris when comedones, papules and pustules are present. A 3-month time horizon was used in the analysis. The clinical evidence used to support the cost-minimisation analysis came from the results of the published and unpublished studies described above which found no statistically significant difference between Epiduo[®] and Duac[®].

The economic analysis compared the acquisition costs of Epiduo[®] 45g and Duac[®] 25g and 50g, presenting results as cost per gram. The cost per day of treatment was also provided. The company provided additional analysis based on the number of tubes used over the 12-week treatment duration. As the treatments are administered at home by patients no administration or monitoring costs were included.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS involved a simple discount on the list price of the gel. The results showed that both with and without the PAS, Epiduo[®] was associated with lower costs per day and per tube and therefore would be the preferred treatment on cost-minimisation grounds.

The following limitations were noted:

- In relation to the treatment likely to be displaced, expert responses were mixed. Various treatment options were mentioned, including Duac[®], Zineryt[®], benzoyl peroxide, retinoids and antibiotics either alone or in combination. However on balance the committee considered Duac[®] to be a reasonable comparator.
- In the scenario analysis the company compared Epiduo[®] with Zineryt[®] and this showed Epiduo[®] to be cost-saving with the PAS. The analysis assumed equivalent efficacy with Zineryt[®] but no clinical evidence was submitted to support this assumption. The company has subsequently provided a simple naive indirect comparison based on available literature. The analysis was considered relatively simple, however it provided some indication of comparable efficacy.
- There was some uncertainty around the amount of Epiduo[®] used in the economic analysis. The company provide scenario analysis varying the dose by $\pm 25\%$. Results indicate that Epiduo[®] is cost saving versus Duac[®] in all scenarios with the PAS.
- There is some evidence to suggest Duac[®] may be better tolerated than Epiduo[®] as it was associated with a lower incidence of dermatological adverse events. The economic analysis did not account for any differences in adverse events which may have introduced a small bias in favour of Epiduo[®].
- The costs of moisturisers were not included. This is unlikely to be a major concern as any expected costs would be likely to be out of pocket and therefore would not impact on the NHS and would not be expected to differ between treatments.

The company has largely addressed the concerns above therefore the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified Patient Information Group.

- A Submission was received from Skin Care Campaign Scotland (SCCC), a Scottish registered charity.
- SCCC has received funding from several pharmaceutical companies in the past two years.
- Acne is almost universal in adolescents, but can occur at any age from infancy onwards. Even in mild form it can be socially disruptive, and particularly when severe can have a major psychosocial impact. It can lead to teasing and bullying, avoidance of sport, exercise and going out, poor self-esteem, all leading to poor performance at school and social isolation. In extreme cases, not necessarily linked to severity of acne, it can lead to

depressive illness, including increased risk of suicide, yet it is often treated as trivial with a “you'll grow out of it” attitude when advice is sought. Even in mild acne there is a risk of permanent scarring, completely avoidable if appropriate treatment is made available promptly.

- Current treatments require time, weeks or months, to take effect, but teenagers particularly find it difficult to stick to treatment regimes and to persevere when improvement seems to be slow. Cream applications are often too greasy, lotions too drying. Side-effects, mainly peeling and inflammation are very common with topical treatments and staining or bleaching of clothing, towels etc., is a further problem that can put people off continuing with treatment. People are also wary of antibiotics, aware of risks of resistance, and less likely to persevere with them.
- This new medication has advantages in ease of application, speed of action, and avoidance of the worst side-effects associated with existing medicines.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries have recommendations for the treatment of acne vulgaris which were revised in July 2013.⁷ For mild acne, this recommends the first-line use of a single topical treatment e.g. topical retinoid (tretinoin, isotretinoin or adapalene) or benzoyl peroxide (particularly if papules and pustules are present). Azelaic acid can be used if topical retinoids and benzoyl peroxide are poorly tolerated. For moderate acne with predominately inflammatory lesions, a single topical treatment (e.g. benzoyl peroxide or a topical retinoid) should be considered for patients with limited acne which is unlikely to scar. Combined treatment e.g. a topical antibiotic plus benzoyl peroxide or a topical retinoid is the preferred option.

The European Academy of Dermatology and Venereology published “European evidence-based (S3) guidelines for the treatment of acne” in 2012 with recommendations based on a systematic review and structured consensus process.⁸ For topical treatment of mild to moderate papulopustular acne, this guideline strongly recommends the fixed-dose combinations of adapalene plus benzoyl peroxide and clindamycin plus benzoyl peroxide, although the latter is limited to a 3 month treatment period. There are medium strength recommendations for azelaic acid, benzoyl peroxide, topical retinoids (adapalene) noting that these agents can be recommended. There are low strength recommendations for the fixed-dose combination of erythromycin plus tretinoin, erythromycin plus isotretinoin noting that these can be considered. The guideline also states that topical antibiotics as monotherapy and the fixed-dose combination of erythromycin and zinc are not recommended for the treatment of mild to moderate papulopustular acne.

Additional information: comparators

Other topical agents for mild to moderate acne including antibiotics.

Cost of relevant comparators

Drug	Dose Regimen	Cost (£)/pack size	Cost per gram or ml (£)
Adapalene 0.1%/benzoyl peroxide 2.5% gel (Epiduo®)	Apply once daily	17.91/45g	0.40
Clindamycin 1%/benzoyl peroxide 5% gel (Duac® once daily)	Apply once daily	9.95/25g	0.40
Clindamycin 1%/benzoyl peroxide 3% gel (Duac® once daily)	Apply once daily	11.94/30g	0.40
Erythromycin 4%/zinc acetate 1.2% topical solution (Zineryt®)	Apply twice daily	7.71/30ml 16.68/90ml	0.26 0.19
Adapalene 0.1% gel	Apply once daily	13.69/45g	0.30
Benzoyl peroxide 2.5% gel (Panoxyl Aquagel®)	Apply once or twice daily	1.76/40g	0.04
Benzoyl peroxide 5% gel (Panoxyl Aquagel®)	Apply once or twice daily	1.92/40g	0.05

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 8 January 2014 except for Panoxyl Aquagel® which is from eMIMs on 8 January 2014. There are supply problems with Panoxyl Aquagel®.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 40,917 from year 1 to year 5.

Without PAS:

The gross impact on the medicines budget was expected to be £364k in year 1 and £1m over 5 years. As other drugs were assumed to be displaced the net medicines budget impact is expected to be savings of £53k in year 1 and £157k over 5 years.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission.

1. Galderma. Epiduo® 0.1%/2.5% gel, summary of product characteristics, 25 July 2013
2. Zouboulis CC, Fischer TC, Wohlrab J et al. Study of the efficacy, tolerability, and safety of 2 fixed-dose combination gels in the management of acne vulgaris. *Cutis* 2009;84:223-9.
3. *Other data were also assessed but remain commercially confidential.**
4. Tan J, Gollnick HP, Loesche C et al. Synergistic efficacy of adapalene 0.1% / benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. *J Dermatolog Treat* 2011;22:197-205.
5. Pariser DM, Westmoreland P, Morris A et al. Long-term safety and efficacy of a unique fixed-dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% for the treatment of acne vulgaris. *J Drugs Dermatol* 2007;6:899-905.
6. Eichenfield LF, Draelos Z, Lucky AW et al. Preadolescent moderate acne vulgaris: a randomized trial of the efficacy and safety of topical adapalene-benzoyl peroxides. *J Drugs Dermatol* 2013;12:611-8.
7. National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries: Acne vulgaris, July 2013 [www.cks.nice.org.uk/acne-vulgaris]
8. Nast A, Dreno B, Bettoli V et al. European evidence based (S3) guidelines for the treatment of acne. *J Eur Acad Dermatol Venereol* 2012;26 Suppl 1:1-29.
9. Stiefel. Duac® once daily 10mg/g and 30mg/g gel, summary of product characteristics, 8 July 2013

This assessment is based on data submitted by the applicant company up to and including 14 February 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group

(PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.