

adapalene 0.1%/benzoyl peroxide 2.5% gel (Epiduo®)

SMC No. (682/11)

Galderma

04 February 2011

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

adapalene 0.1%/benzoyl peroxide 2.5% gel (Epiduo®) is not recommended for use within NHS Scotland.

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

In a 12-week study in patients with severe acne also receiving oral doxycycline, adapalene 0.1%/benzoyl peroxide 2.5% gel reduced the total lesion count compared with vehicle gel. A 24-week extension study showed a higher rate of maintenance success with adapalene 0.1%/benzoyl peroxide 2.5% gel versus vehicle gel alone.

The clinical and economic case was based on patients with severe acne who refuse treatment with, or have a contraindication to, oral isotretinoin. Comparative efficacy versus alternative treatment options in this patient group is unclear.

As a consequence, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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 areas 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.

Product availability date

21 May 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 that may be less irritant than topical retinoids. Benzoyl peroxide is also commonly used in mild to moderate acne and has antimicrobial, exfoliative and keratolytic properties. Epiduo[®] gel is a fixed ratio, once daily combination preparation of adapalene 0.1%/benzoyl peroxide 2.5% gel with anti-comedogenic, comedolytic, anti-inflammatory and bactericidal properties.

Adapalene 0.1%/benzoyl peroxide 2.5% gel has a marketing authorisation for the cutaneous treatment of acne vulgaris when comedones, papules and pustules are present. The manufacturer has requested that SMC considers the use of adapalene 0.1%/benzoyl peroxide 2.5% gel positioned for use in a sub-population of the licensed indication, namely in patients with severe acne who refuse treatment with, or have a contraindication to, oral isotretinoin.

Four randomised, double-blind, superiority studies provide evidence for the efficacy of adapalene 0.1%/benzoyl peroxide 2.5% gel. Two were similarly designed 12-week studies, comparing adapalene 0.1%/benzoyl peroxide 2.5% gel with adapalene and benzoyl peroxide administered separately in patients with all severities of acne and moderately severe acne respectively. Another 12-week study compared doxycycline treatment in combination with either adapalene 0.1%/benzoyl peroxide 2.5% gel or vehicle gel in patients with severe acne. The fourth study was an unpublished 24-week maintenance treatment extension of the 12-week study.

Comparison with individual constituents

A phase II study enrolled 517 patients with all degrees of acne severity and randomised them to receive either adapalene 0.1%/benzoyl peroxide 2.5% gel (n=149), adapalene 0.1% gel (n=148), benzoyl peroxide 2.5% gel (n=149) or vehicle gel (n=71). The primary endpoint of success (assessed using an Investigators Global Assessment (IGA) 5-point scoring system and defined as reaching a score of 0 (clear) or 1 (almost clear) on the scale) was achieved by 28% of the adapalene 0.1%/benzoyl peroxide 2.5% gel group, 16% of the adapalene group, 15% of the benzoyl peroxide group and 9.9% of the vehicle gel group, with the adapalene 0.1%/benzoyl peroxide 2.5% gel group showing superiority over all other groups. Similar results were

reported for the other primary end-points of reductions in inflammatory lesion count, non-inflammatory lesion count and total lesion count.

A phase III study randomised 1,668 patients with acne of moderate severity (IGA score of 3) to receive adapalene 0.1%/benzoyl peroxide 2.5% gel (n=415), adapalene 0.1% gel (n=420), benzoyl peroxide 2.5% gel (n=415) or vehicle gel (n=418). Success rate (defined as an improvement of 2 points on a 5-point IGA scale) was 30%, 20%, 22% and 11% in each of the groups, respectively. The adapalene 0.1%/benzoyl peroxide 2.5% gel was found to be superior to all other treatments with similar results for reductions in non-inflammatory and total lesion counts. For reductions in inflammatory lesion count, the adapalene 0.1%/benzoyl peroxide 2.5% gel was found to be superior to adapalene and gel vehicle groups, but not to benzoyl peroxide gel.

Combination with oral antibiotic in severe acne

In a 12-week study, 459 patients aged 12 to 35 with severe facial acne, defined as a score of 4 on a 6-point IGA scale (where 0=clear and 5=very severe) were randomised to receive either adapalene 0.1%/benzoyl peroxide 2.5% gel or vehicle gel, to be applied to the face once daily in the evening. In addition, all patients received oral doxycycline 100mg in the morning. The primary endpoint, analysed in the intent-to-treat (ITT) population, using the last observation carried forward method, was the percentage change from baseline in the total lesion count (sum of inflammatory and non-inflammatory lesions) at week 12. Secondary endpoints included the percentage change in total lesion count at each visit, percentage changes in inflammatory and non-inflammatory lesions and success rates, based on IGA scores, where success equalled scores of “clear” or “almost clear”.

The median decrease in the total lesion count was 64% for the patients receiving adapalene 0.1%/benzoyl peroxide 2.5% gel and 41% for the group receiving vehicle gel. This difference was statistically significant and demonstrated that doxycycline combined with the adapalene 0.1%/benzoyl peroxide 2.5% gel was superior to vehicle gel and doxycycline at week 12. The regimen including the adapalene 0.1%/benzoyl peroxide 0.25% gel was significantly more effective at each visit, with regard to total lesion counts, inflammatory lesion counts and non-inflammatory counts. At week 12, the IGA-defined success rate for the combined doxycycline with adapalene 0.1%/benzoyl peroxide 2.5% regimen was significantly greater than for the vehicle plus doxycycline group (32% and 8.4% respectively). A patient satisfaction questionnaire showed that significantly more patients treated with the regimen including the adapalene 0.1%/ benzoyl peroxide 2.5% gel were satisfied with their treatment.

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

Summary of evidence on comparative safety

Overall, the safety and tolerability of adapalene 0.1%/benzoyl peroxide 2.5% gel was similar to vehicle gel.

In the 12-week combination study with doxycycline, treatment-related adverse events (AEs) occurred in 11% of the patients treated with adapalene 0.1%/benzoyl peroxide 2.5% gel and in 12% of those who received vehicle. Adverse events were primarily due to the doxycycline, with gastrointestinal disorders occurring in 9.6% of all participants. Three patients in the vehicle group discontinued because of gastrointestinal disorders and three discontinued due to

dermatological events (two in the adapalene 0.1%/benzoyl peroxide 2.5% group and one in the vehicle group). Dermatological AEs were reported in both groups: 1.7% of patients in the adapalene 0.1%/ benzoyl peroxide 2.5% group reported dryness, irritation and eyelid irritation and 0.4% in the vehicle group reported urticaria.

Summary of clinical effectiveness issues

Two randomised controlled studies of adapalene 0.1%/benzoyl peroxide 2.5% gel in a total of 2385 patients have shown that this combination gel provided a greater net benefit in patients with all grades of acne than the individual constituents given separately. The mechanism of this synergistic effect is unclear.

The manufacturer has requested that SMC considers the use of adapalene 0.1%/benzoyl peroxide 2.5% gel when positioned for the treatment of severe acne in patients who refuse treatment with, or who are contraindicated to, oral isotretinoin. Oral isotretinoin is an established treatment for severe acne but is associated with a number of serious adverse effects, including teratogenicity; in addition patients require regular monitoring of hepatic function and serum lipids.

To support this positioning a study in patients with severe acne treated with doxycycline plus either adapalene 0.1%/benzoyl peroxide 2.5% gel or vehicle was presented. Although the study showed a greater decrease in the total lesion count with the combination gel, there are a number of limitations with this study. SMC clinical experts suggest that treatment options for severe acne include oral antibiotics in combination with a topical retinoid and/or benzoyl peroxide. The comparator to adapalene 0.1%/benzoyl peroxide 2.5% gel in this study was placebo providing no comparative data versus a topical retinoid, or adapalene with or without benzoyl peroxide. No patients were identified who specifically had refused treatment with isotretinoin or who were contraindicated to it. However, the manufacturer suggests that this group of patients is indistinguishable from all other patients with severe acne. SMC experts advise that this population is likely to be small.

In the extension phase maintenance study, there was a difference in baseline characteristics between the two groups, with patients in the adapalene 0.1%/benzoyl peroxide 2.5% gel group having more severe disease (27% of patients were clear or almost clear of acne versus 38% of the vehicle group). There was higher drop out rate in the vehicle group (35% compared with 15%) and this was mainly due to patient request.

Because of the lack of comparative data, an indirect comparison using the Bucher method was presented, which was pivotal to the economic case. The indirect comparison included the four studies submitted which were relevant and of reasonable quality. The results indicate that treatment with adapalene 0.1%/benzoyl peroxide 2.5% is associated with reduced treatment discontinuation and increased 12-week and maintenance response compared to adapalene. Confidence intervals around the log odds ratios indicate that differences were significant only for the acute response rate. As already discussed, it may have been more relevant to compare adapalene 0.1%/benzoyl peroxide 2.5% with another topical retinoid or with adapalene in combination with benzoyl peroxide. Statistical advice indicated that a mixed treatment comparison may have been appropriate.

For patients who require both adapalene and benzoyl peroxide, this combination product, with once daily dosing, would simplify the treatment regimen and may be expected to improve patient adherence. However, SMC clinical experts have questioned the positioning proposed by the manufacturer for adapalene 0.1%/benzoyl peroxide 2.5% gel. They advised that the population of patients with severe acne who refuse treatment with, or who are contraindicated to, oral isotretinoin is likely to be very small. Clinical experts suggested that this preparation would be more likely to be used in patients with less severe acne.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis of adapalene 0.1%/benzoyl peroxide 2.5% gel used in combination with an oral antibiotic for patients with severe acne. The comparator was treatment with adapalene plus an oral antibiotic. The model had a one year time horizon; for both treatment strategies combined oral and topical treatment was given for six months for patients who responded or partially responded to treatment at 3 months. At six months, the oral antibiotic could be removed in responding patients and followed by 6 months of topical treatment with either adapalene 0.1%/benzoyl peroxide 2.5% gel or adapalene. The patients in the model were a subset consisting of patients with severe acne who refuse treatment with, or are contraindicated to, oral isotretinoin.

Clinical data to drive the results of the economic model were taken from an indirect comparison using the Bucher method. The results of the indirect comparison indicated superior response rates for adapalene 0.1%/benzoyl peroxide 2.5% gel than the comparator treatment. Quality of life values were estimated from a published study and indicated that a patient who responded to treatment would have quality of life that was 5% better than a patient who did not respond.

The results of the analysis showed an incremental cost per quality adjusted life year (QALY) of £6,456 based on an incremental cost of £4 and a QALY gain of 0.0057. Sensitivity analysis showed that the results were most sensitive to the QALY gain. If the gain in quality of life with response was only 2% the ICER rose to £32, 280, however the base case gain in quality of life did seem reasonable. The results were also sensitive to the odds ratios estimated from the indirect comparison.

There were a number of weaknesses or uncertainties associated with the analysis:

- A key weakness was the failure to compare adapalene 0.1%/benzoyl peroxide 2.5% gel with other relevant comparator treatment options. For example, there was no comparison with adapalene and benzoyl peroxide given separately in combination with an oral antibiotic to help demonstrate the cost-effectiveness of the combination product over the component drugs. Sensitivity analysis using the cheaper topical retinoid tretinoin rather than adapalene raised the cost effectiveness ratio to £11,576 per QALY.
- An indirect comparison was conducted using the Bucher method, however a mixed treatment comparison may have been more appropriate.
- The duration of treatment with oral and topical treatment was 6 months whereas only 3 months was used in the clinical trial. The model showed some sensitivity to different treatment pathways being used.

Given these issues, the economic case has not been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Skin Care Campaign Scotland (SCCS)

Additional information: guidelines and protocols

The NHS Clinical Knowledge Summaries have recommendations for the treatment of acne vulgaris. These include use of combinations of oral antibiotics and topical retinoids or benzoyl peroxide.

“European recommendations on the use of oral antibiotics for acne” was published in 2004 and recommend second generation cyclines as the antibiotic of choice, to be used for 3 months. They should not be used alone, but in combination with a topical retinoid. If longer treatment is needed, benzoyl peroxide or similar should be added in. For maintenance therapy, topical retinoids are the treatment of choice and benzoyl peroxide can be added in.

The NHS Scotland National Patient Pathway for acne recommends oral isotretinoin if oral antibiotics have not worked (at least 6 months treatment with one or two antibiotics plus topical therapy).

Additional information: comparators

Treatment for severe acne would include topical retinoids (e.g. isotretinoin, tretinoin and the retinoid-like adapalene) in combination with oral antibiotics (e.g. oxytetracycline, doxycycline, lymecycline, minocycline and erythromycin) or oral isotretinoin. Benzoyl peroxide can be added to the combination of topical retinoid and oral antibiotic.

Cost of relevant comparators

Drug	Dose Regimen	Cost	Cost per gram (£)
Topical retinoids and retinoid-like agents			
adapalene 0.1%/benzoyl peroxide 2.5%	apply once daily	£17.91/45g	0.40
adapalene gel or cream 0.1%	apply once daily	£11.40/45g	0.25
isotretinoin gel 0.05%	apply once or twice daily	£5.94/30g	0.20
tretinoin 0.01% and 0.025% gel	apply once or twice daily	£5.28/60g	0.09
Topical agents			
benzoyl peroxide 2.5% aqueous gel	apply once or twice daily	£1.76/40g	0.04

Oral antibiotics			
doxycycline	100mg daily for 3 months	£5	-
oxytetracycline	500mg twice daily for 3 months	£15	-
Oral isotretinoin			
isotretinoin capsules	500micrograms/kg to 1mg/kg daily, for 16 to 24 weeks (maximum 150mg/kg per course), *	30 to 384	-

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2 December 2010, except for benzoyl peroxide gel which is from the British National Formulary number 60 (September 2010). Note that oral antibiotics can be used in combination with topical retinoids and benzoyl peroxide can be added as a third agent. Benzoyl peroxide comes as other strengths, but for the purposes of comparison, the concentration in the adapalene/benzoyl peroxide gel was used. Cost of topical treatment will depend on skin area to be covered.*This course of oral isotretinoin can be repeated after 8 weeks, if needed. Costs are based on a 70kg patient.

Additional information: budget impact

The manufacturer estimated a net drug budget impact in year one of £12k rising to £58k in year five. The manufacturer assumed that 3776 patients would fall into the subset specified and that 10% of the eligible patients would receive treatment with adapalene 0.1%/benzoyl peroxide 2.5% gel plus oral antibiotic in year one rising to 50% by year five, to give 378 patients treated in year one rising to 1888 patients in year five. These estimates assume that use is restricted to patients in the positioning proposed by the manufacturer i.e. only in patients with severe acne who refuse treatment with or who are contraindicated to oral isotretinoin.

References

The undernoted references were supplied with the submission.

Stein Gold L, Cruz A, Echenfield L, Tan J. Effective and safe combination therapy for severe acne vulgaris: A randomised, vehicle-controlled, double-blind study of adapalene 0.1%, benzoyl peroxide 2.5% fixed dose combination gel with doxycycline hyclate 100 mg. *Cutis*. 2010; 85: 94-104.

Stein Gold L, Tan J, Cruz A. A North American Study of Adapalene-Benzoyl Peroxide Combination Gel in the Treatment of Acne. *Cutis*. 2009;84:110-6.

Thiboutot DM, Weiss J, Bucko A et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol*. 2007 Nov;57(5):791-9.

**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/>*

This assessment is based on data submitted by the applicant company up to and including 13 January 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.

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.