Scottish Medicines Consortium

betamethasone valerate 2.25mg medicated plaster (Betesil®)
No. (622/10)

Genus Pharmaceuticals

09 July 2010

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

betamethasone valerate medicated plaster (Betesil®) is not recommended for use within NHS Scotland.

Indication under review: Treatment of inflammatory skin disorders which do not respond to treatment with less potent corticosteroids, such as eczema, lichenification, lichen planus, granuloma annulare, palmoplantar pustulosis and mycosis fungoides. Due to its particular pharmaceutical form, betamethasone medicated plaster is suitable for chronic plaque psoriasis localized in difficult to treat areas (e.g. knees, elbows and anterior face of the tibia on an area not greater than 5% of the body surface).

In phase III studies in patients with mild to moderate plaque psoriasis, betamethasone medicated plaster was superior to non-occluded betamethasone cream, assessed using the psoriasis area and severity index score and psoriasis global assessment.

However, the manufacturer did not submit a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of inflammatory skin disorders which do not respond to treatment with less potent corticosteroids, such as eczema, lichenification, lichen planus, granuloma annulare, palmoplantar pustulosis and mycosis fungoides. Due to its particular pharmaceutical form, betamethasone medicated plaster is suitable for chronic plaque psoriasis localized in difficult to treat areas (e.g. knees, elbows and anterior face of the tibia on an area not greater than 5% of the body surface).

Dosing information

Apply the medicated plaster to the skin area to be treated once a day. Do not exceed the maximum daily dose of six medicated plasters and the maximum treatment period of 30 days. A new medicated plaster must be applied every 24 hours; It is also advisable to wait at least 30 minutes between one application and the next.

Product availability date

12 March 2007

Summary of evidence on comparative efficacy

Betamethasone medicated plaster 0.1% is a topical plaster formulation available in a 10cm by 7.5cm size containing 2.25mg of betamethasone valerate. The plaster may be cut to fit the area of skin being treated and the unused plaster used within one month.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication, namely patients with chronic plaque psoriasis.

Two randomised comparator controlled studies of differing designs have been undertaken comparing betamethasone medicated plaster 0.1% with non-occluded betamethasone cream 0.1% in patients with plaque psoriasis. The randomised assessor-blind paired comparison study recruited 42 patients with paired lesions >1cm in diameter in similar anatomical locations and with a surface area < 75cm^2. Each patient acted as their own control with one bilateral lesion being treated with betamethasone medicated plaster 0.1% and the other with betamethasone valerate 0.1% cream applied daily for 30 days. The main efficacy assessment used the psoriasis area and severity index (PASI) and the self- administered PASI (SAPASI) scores which were documented at baseline and end of study. Treatment response was defined as ≥75% decrease in PASI score from baseline to end of study. The PASI scores were determined by a blinded observer and were based on upper extremities, lower extremities, and trunk body areas, giving a total score range of 0 to 72. The SAPASI score, assessed by the patient, was the summation of scores for erythema, scales and infiltration of each lesion to produce a total score (range 0 to 30). Quality of life was assessed through a patient self-completed questionnaire.

At baseline the PASI scores were 16.4 (standard deviation 10.6) and 16.5 (10.3) for the cream and medicated plaster respectively. After 30 days treatment, the scores had reduced to 10.1 (8.1) in the cream and 6.3 (7.7) in the plaster groups; a 38% versus 62% reduction ($p<0.001$). At baseline SAPASI scores for the cream and plaster groups were 19.4 (4.1) and 19.4 (4.5) respectively, and were reduced to 12.8 (6.2) and 7.9 (5.5) at the end of the study; a 34% versus 59% reduction ($p<0.001$). A treatment response was observed in 12% and 38% of lesions treated with cream and medicated plaster respectively ($p=0.011$). In terms of

quality of life there was significantly higher cosmetic acceptability and tolerability for the medicated plaster than cream. In addition, patients who preferred the medicated plaster specified that it was easier to apply than the cream.

The second study, currently published in poster form only, was an open (assessor blind) controlled study recruiting 231 patients with chronic stable plaque psoriasis. At least two target lesions with a surface area >10cm^2 and <150cm^2 were selected for treatment. Each patient was randomised to treatment with betamethasone valerate 0.1% cream applied twice daily or betamethasone medicated plaster (2 to 8 plasters). The primary outcome efficacy endpoint was the proportion of patients for whom disappearance of active lesions could be documented after 3 weeks as assessed by blinded assessors (on standardised photographs of target skin areas) and based on the psoriasis global assessment (PGA) score (0=cleared to 5=severe psoriasis). Secondary endpoints included disappearance of active lesions as measured by PGA after 5 weeks treatment (assessed by blind assessors); and disappearance of active lesions as measured by PGA after 3 and 5 weeks treatment (assessed by principal investigators and patients). In addition, acceptability of treatment by the patients was measured on a 10-point scale (0=zero to 10=excellent).

The PGA score at baseline for patients treated with betamethasone cream and medicated plaster respectively was; 2 (17% vs. 12%); 3 (50% vs. 56%); 4 (23% vs. 25%); and 5 (11% vs. 6.9%). The percentage of patients for whom the disappearance of the active lesions could be documented after 3 weeks treatment was 31% versus 53% for betamethasone cream and medicated plaster respectively ($p<0.001$). At 5 weeks the percentages were 40% versus 58% respectively ($p=0.006$). Investigator and patient's assessment also resulted in significant differences in favour of the medicated plaster group. There were no significant differences between betamethasone medicated plaster and cream with respect to local tolerability. The level of acceptability and patient satisfaction was, however, significantly higher for the medicated plaster compared with cream although the cream was preferred in terms of ease of use.

Summary of evidence on comparative safety

In the first study the authors reported that no adverse events occurred during the study with none of the treated lesions showing signs of irritation, and subjects tolerated both treatments well. In the second study similar numbers of patients in the two groups experienced adverse events (12%). Nasopharyngitis (3.5% versus 2.6%), headache (1.8% versus 2.6%) and contact dermatitis (0% versus 1.7%) were experienced by >1% of patients in either group for betamethasone cream and medicated plaster, respectively.

Summary of clinical effectiveness issues

The European Medicines Agency (EMA) has produced guidance for the clinical investigation of medicinal products indicated for the treatment of psoriasis although this came into effect after the main published study had begun. They recommend a study duration of 4 weeks for a potent topically applied corticosteroid to show short-term efficacy. They consider that the PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment and recommend the use of two endpoints to assess efficacy: a validated, standardised global score (e.g. PGA) in conjunction with PASI.

The key studies demonstrated a significant effect on PASI and PGA scores (in the first and second studies respectively) for betamethasone medicated plaster versus non-occluded cream. There were, however, a number of limitations with the studies: there were no

apparent power calculations for sample size; primary endpoints did not concur with EMA guidance; there was no placebo plaster arm; confidence intervals were not reported and there were small patient numbers in one study. In addition, only limited details and errors (in one study) were included in the published reports.

In the first study there are some data to suggest that patients considered the medicated plaster to have higher cosmetic acceptability and tolerability than the cream formulation. In the second study patients reported that the (non-occluded) cream was easier to use than the plaster although the overall level of acceptability and satisfaction was higher for the plaster.

The use of occlusion improves the effectiveness of corticosteroids. Both the key studies used non-occluded betamethasone 0.1% cream (administered once and twice daily in the studies respectively) as a comparator. There are three phase II studies comparing betamethasone medicated plaster with occluded betamethasone cream/ointment, two of which were conducted in healthy volunteers and measured vasoconstrictor and anti-inflammatory properties. The only study comparing betamethasone medicated plaster with occluded cream had significant weaknesses: the comparison with active treatment was a secondary objective and was not double-blind; the total application time for all treatments was 96 hours. In this study occluded betamethasone cream achieved a greater reduction in the PASI score than the betamethasone medicated plaster.

Betamethasone medicated plaster may have advantages in that a measurable dose of corticosteroid is delivered, compared with the use of occluded cream/ointment where the precise dose delivered is not be known and may be over-applied.

Recommendations for the initial management of psoriasis produced by the British Association of Dermatologists in association with the Primary Care Dermatology Society note that the use of topical steroids may lead to rebound exacerbation when treatment is discontinued. In the second phase III study follow-up was reported and it was noted that of the patients who achieved a complete remission approximately 12% in each group had rebound/relapse; this occurred with a median time of 43 days for the medicated plaster and 36 days for the cream.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing the daily costs of betamethasone medicated plaster to various corticosteroid creams and ointments (non-proprietary beclometasone valerate 0.1%, Betnovate®, Synalar® and Locoid®/Lipocream®) under occlusive dressings for the treatment of mild to moderate chronic plaque psoriasis localized in difficult to treat areas (e.g. knees, elbows and anterior face of the tibia on an area not greater than 5% of the body surface). A three month treatment period was defined.

The manufacturer assumed clinical equivalence/non-inferiority of plaster and comparators based on the two efficacy studies that compared betamethasone medicated plaster to betamethasone valerate non-occluded cream and three phase II studies (two conducted in healthy volunteers). The analysis compared the cost-per-day to treat an average patient, defined as having two lesions treated with betamethasone medicated plaster to the average cost for application of cream plus the cost of an occlusive dressing added (DuoDerm®). Compared to the other potent topical corticosteroids under occlusive dressing, the manufacturer claimed that betamethasone medicated plaster was cost- effective.

The main limitations of the analysis were:

- The results presented by the manufacturer showed that betamethasone medicated plaster was generally not the preferred treatment on cost-minimisation grounds. For example, the results indicated that non-proprietary betamethasone valerate 0.1% cream applied once daily plus occlusion costs £2.45, and similarly, the cost-per-day for Betnovate® applied once daily, plus occlusion to be £2.44. As the cost-per-day for betamethasone medicated plaster is £4.96, betamethasone medicated plaster is therefore not cost effective. Even when compared to both of these creams applied twice daily plus occlusion, betamethasone medicated plaster is still marginally more expensive as the cost-per-day is £4.90 and £4.89 for betamethasone valerate 0.1% cream and Betnovate® respectively. Only in situations where three or more occlusive dressings per lesion per day are required for the comparator treatments (e.g. Synalar® which may be applied three times daily) was betamethasone medicated plaster the preferred treatment on cost-minimisation grounds.
- The absence of robust clinical evidence to support the assumption of clinical equivalence/non-inferiority between betamethasone medicated plaster and creams under occlusion in patients with mild-to-moderate chronic plaque psoriasis (including in difficult to treat areas including the knees and elbows).
- The views of SMC clinical experts questioning the appropriateness of creams or ointments under occlusion as the comparator currently used in clinical practice in Scotland, and if comparing betamethasone medicated plaster to the non-occluded creams, betamethasone medicated plaster was not cost-effective.

In conclusion, the economic case for betamethasone medicated plaster has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was received from PSALV, Psoriasis Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) are currently developing a new guideline on the diagnosis and management of psoriasis and psoriatic arthritis with an estimated publication date of winter 2010.

The British Association of Dermatologists in association with the Primary Care Dermatology Society produced recommendations for the initial management of psoriasis in 2003. This guidance predates the availability of betamethasone medicated plaster. For treatment of localised plaque psoriasis a range of treatment options are listed including tar-based cream or tar-based/corticosteroid mixture, moderate potency topical steroid, vitamin D analogue, calcipotriol with betamethasone diproprionate, vitamin A analogue and a dithranol preparation.

Additional information: comparators

Comparators are topical potent corticosteroid preparations and include betamethasone valerate 0.1% cream or ointment, betamethasone dipropionate 0.05% cream or ointment (including calcipotriol/betamethasone dipropionate ointment [Dovobet]), hydrocortisone butyrate 0.1% cream or ointment, mometasone furoate 0.1% cream or ointment, diflucortolone valerate 0.1% cream or ointment and flucinonide 0.05% ointment. Some

preparations may be applied with occlusion. In addition fludroxycortide is available as a tape formulation, although it is considered of moderate potency.

Cost of relevant comparators

Drug	Dose regimen	Cost per day (£)*
Betamethasone medicated plaster	**Apply one plaster each day**	**2.48**
Betamethasone 0.05%/calcipotriol 50 micrograms/g (Dovobet) ointment	Apply once or twice daily	2.36 to 4.71
Fludroxycortide 4 micrograms/cm^2 (Haelan) tape	Cut to size and apply for 12 out of 24 hours	1.85
Mometasone furoate 0.1% (Elocon) cream/ointment	Apply once daily	0.53 to 0.62
Flucinonide 0.05% (Metosyn) ointment	Apply once or twice daily	0.50 to 1.00
Betamethasone diproprionate 0.05% (Diprosone) cream/ointment	Apply once or twice daily	0.31 to 0.62
Diflucortolone valerate 0.1% (Nerisone) cream/ointment	Apply once or twice daily	0.23 to 0.46
Hydrocortisone butyrate 0.1% (Locoid) cream/ointment	Apply once or twice daily	0.22 to 0.46
Betamethasone valerate 0.1% (Betnovate) cream/ointment	Apply once or twice daily	0.20 to 0.41

Doses are for general comparison and do not imply therapeutic equivalence. Costs obtained from eVadis on 28 April 2010.

* Cost for betamethasone medicated plaster based on use of one per day (NB; up to six per day may be used depending on area to be treated for maximum treatment duration of 30 days).

Cost for fludroxycortide tape based on a 7.5cm x 10cm size.

Cost per day for creams/ointments are very approximate and are based on the use of 30g to 60g per week and do not include occlusion dressings. Cost of DuoDerm extra thin dressing (10cm^2) is £1.23.

Additional information: budget impact

The manufacturer stated there to be no net resource implications associated with betamethasone medicated plaster. Approximately 500 patients were estimated by the manufacturer to be eligible for treatment in year one, rising to 2,500 by year five. Note that the cost-neutral budget impact is based on the findings of the cost-minimisation analysis presented by the manufacturer. As noted above, betamethasone medicated plaster was not a cost-minimising treatment against all comparators thus the budget impact may not be cost neutral.

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.

This assessment is based on data submitted by the applicant company up to and including 18 June 2010.

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.

The undernoted references were supplied with the submission.

Pacifico A, Daidone R, Peris K A new formulation of an occlusive dressing containing betamethasone valerate 0.1% in the treatment of mild to moderate psoriasis. J Eur Acad Dermatol Venereol. 2006; 20: 153-157.

Naldi L, Braathen L, Kaszuba A and Ortonne J-P. Poster presented 2nd World Psoriasis & Psoriatic Arthritis Conference (International Federation of Psoriasis Associations), Stockholm, Sweden, 24-28 June 2009; Poster ref. #56 and oral presentation at European Academy of Dermatology and Venereology (EADV) Congress in Berlin, Oct 6-11, 2009

Naldi L Study summary for Multicentric, prospective, single blind, randomized study in parallel, controlled groups versus betamethasone valerate cream, to confirm the efficacy and safety of BETESIL® 0.1%, medicated plaster in the treatment of chronic plaque psoriasis (Study code 04EU/BMT06, IBSA 2009).

Committee for Medicinal Products for Human Use. Guidelines on clinical investigation for medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr. 18 November 2004. www.ema.europa.eu [last accessed 20/4/10]