Scottish Medicines Consortium

Re-submission

Calcipotriol and betamethasone dipropionate ointment (Dovobet®)

Leo Pharma **(No. 09/02)**

04 November 2005

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 resubmission

Calcipotriol/betamethasone dipropionate ointment (Dovobet®) is accepted for restricted use within NHS Scotland for the initial topical treatment of stable plaque psoriasis. Short-term comparisons have shown that the combination is more effective than either component as monotherapy and that it is cost effective compared to alternative therapies.

Its use is restricted to physicians experienced in treating inflammatory skin disease. Dovobet contains a potent steroid, the use of which carries risks of destabilising psoriasis and side effects from prolonged use. The duration of treatment should not exceed four weeks.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Calcipotriol and betamethasone dipropionate ointment (Dovobet®)

Indication

The initial topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy.

Dosing information

Applied to the affected area once daily. The maximum daily dose should not exceed 15g, the maximum weekly dose should not exceed 100g and the treated area should not be more than 30% of the body surface area. The recommended duration of treatment should not exceed 4 weeks and there is no experience of repeated use.

UK launch date

May 2002

Comparator medications

Other topical antipsoriatic therapies including other vitamin D analogues (tacalcitol, calcitriol), topical corticosteroids, coal tar, dithranol cream as short contact therapy, topical retinoids.

Cost of relevant comparators

The relative costs will vary according to the amount of product used, which will depend on the size of the area to the treated, the number of daily applications and treatment duration.

Approved name	**Proprietary name**	**Dosing regimen ***	**Unit cost MIMS August 2005**	**Cost/gram**
Betamethasone diprop./ Calcipotriol	Dovobet®	Once daily (max 100g/wk)	£35.00/60g	£0.58
Calcipotriol	Dovonex®	Once or twice daily (max 100g/wk)	£12.02/60g; £24.04/120g	£0.20
Calcitriol	Silkis®	Twice daily (max 30g daily)	£5.76/30g £16.34/100g	£0.16-£0.19
Tacalcitol	Curatoderm®	Once daily (max 10g/daily)	£15.09/30g £26.06/60g £34.75/100g	£0.35- £0.50
Tazarotene	Zorac®	Once daily	0.05% £14.09/30g 0.1% £14.80/30g	£0.47-£0.49
Betamethasone valerate.	Betnovate®	Once or twice daily	£1.43/30g £4.05/100g	£0.04-£0.05
Betamethasone diprop.	Diprosone®	Once or twice daily	£2.24/30g £6.36/100g	£0.06-£0.07
Hydrocortisone butyrate	Locoid®	Once or twice daily	£2.29/30g £7.05/100g	£0.07-£0.08
Mometasone	Elocon®	Once daily	£4.54/30g £13.07/100g	£0.13-£0.15
	Carbo-Dome®	Two-three times daily	£16.38/100g	£0.16
Dithranol 2%	Dithrocream®	One hour application	£7.10/50g	£0.14
Dithranol, coal tar, salicylic acid	Psorin®		£4.41/25g £16.35/100g	£0.16-£0.18

* Dosage regimens based on BNF advice of no more than twice daily application.

Summary of evidence on comparative efficacy

Psoriasis is a chronic skin disorder which affects 1-2% of the UK population. There are several forms of psoriasis but the most common is psoriasis vulgaris or plaque psoriasis which is characterised by well defined, red, raised, scaly lesions. Most cases are mild but the extent of affected skin can range from trivial to almost total coverage and the course of the disease is characterised by relapses and remissions.

Dovobet® contains the vitamin D analogue, calcipotriol, and the potent corticosteroid, betamethasone dipropionate, and was originally launched in May 2002 for twice daily use but was not recommended for use by SMC. This resubmission attempts to address the cost-effectiveness of the product under its now once daily dosing regimen.

The efficacy is supported by the results of two 4-week studies comparing the combination once daily with its components as monotherapy, an 8-week comparison with tacalcitol, another vitamin D analogue and a 12-week comparison with intermittent therapy and calcipotriol. Efficacy was assessed using the Psoriasis Area and Severity Index (PASI) which considers redness, thickness and scaliness of lesions as well as the area affected to give a total score ranging from 0 to 72. The studies conducted used a modified version of the PASI which excluded the head (range 0 to 64.8). The primary endpoint was the reduction in PASI at 4 weeks for all studies except one which used values at 8 weeks.

Dovobet® resulted in greater percentage reductions in the PASI than comparators. When applied daily for 4 weeks, Dovobet® resulted in mean reductions in PASI of 65-71% compared to 59% for calcipotriol twice daily, 46% for calcipotriol once daily, 57% for betamethasone dipropionate once daily and 33% for tacalcitol once daily ($p<0.001$). Similar patterns of response were seen in the secondary endpoints including the percentage of responders (those with an investigator-assessed marked improvement or clearance).

In one of the two efficacy studies, which continued beyond 4 weeks, Dovobet® daily for 4 weeks was followed by calcipotriol daily for 4 weeks and compared to tacalcitol daily for 8 weeks. The primary endpoint, reduction in PASI at 4 weeks, was 65% versus 33% respectively, and at 8 weeks, a secondary endpoint, 59% versus 39% respectively ($p<0.001$ for both comparisons). The other study compared Dovobet® once daily for 8 weeks followed by calcipotriol once daily for 4 weeks with Dovobet® once daily for 4 weeks followed by intermittent therapy for 8 weeks (intermittent: calcipotriol daily on weekdays and Dovobet® daily at weekends) or calcipotriol daily for all 12 weeks. The mean reduction in PASI was significantly greater in the group receiving 8 weeks of Dovobet® initially ($p=0.016$). However, this exceeds the maximum recommended duration of 4 weeks.

Quality of life was assessed in one of the above studies and reported separately. Dovobet® once daily was significantly superior to calcipotriol twice daily in improving quality of life as measured by a general health state measure (EQ-5D VAS score) ($p<0.05$). In terms of a more specific psoriasis disease index, Dovobet® once and twice daily significantly improved quality of life compared to vehicle ($p<0.001$). There was no significant difference reported between Dovobet® twice daily and once daily and calcipotriol twice daily ($p>0.1$). The significance of the difference between Dovobet® once and calcipotriol twice daily was not reported.

An additional long-term study compared Dovobet® once daily as required for 52 weeks (group 1, n=212), Dovobet® once daily for 4 weeks as required alternating with 4 weeks of once daily treatment with calcipotriol as required for 52 weeks (group 2, n=213) and Dovobet® once daily as required for 4 weeks followed by 48 weeks of calcipotriol once daily as required (group 3, n=209). The primary outcome of this study was tolerability. However,

global efficacy was assessed as a secondary endpoint and there was a trend towards a better response to treatment with Dovobet® for 52 weeks than with Dovobet® for 4 weeks then calcipotriol for 48 weeks.

The submission used the PASI ≥ 75%, calculated on a post-hoc basis, as a main efficacy measure for the economic model.

Summary of evidence on comparative safety

Tolerability of Dovobet® during studies was generally good with the most frequently reported drug-related adverse events being lesional/perilesional reactions (2.9-9.9% at 4 weeks). The most common of these was pruritus (reported at 2.6% in one study). Tolerability was assessed during the one-year safety study.There were significantly fewer adverse events reported in the group treated with Dovobet® for 52 weeks than the group who received 4 weeks of Dovobet® and then 48 weeks of calcipotriol ($p<0.001$). Corticosteroid-related adverse events were reported in 4.8% of patients treated with Dovobet® for 52 weeks. Nevertheless, this long-term use is outwith the licence.

Summary of clinical effectiveness issues

The studies conducted are mainly of short duration, 4 weeks, and provide no information on the longer-term effect on this relapsing, remitting condition. Furthermore, the product licence recommends a maximum duration of 4 weeks therapy. This limits the licensed use of Dovobet® in clinical practice.

The main outcome measure was the PASI, which, while widely used, has limitations. The Committee for Medicinal Products for Human Use has advised that the PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment and strongly recommends the use of two endpoints to assess efficacy: a validated, standardised global score in conjunction with PASI. The clinical significance of observed changes in PASI are not always well understood. In clinical trials using PASI, both >50% and >75% improvements compared to baseline have been considered as clinically meaningful. Clear or almost clear has been defined as an improvement of PASI >90%. In general, the best evidence of efficacy is the percentage of patients who achieve the results of “clear or almost clear” (PASI >90%) on treatment. This would correspond to the “responders” in the discussed studies. However the manufacturer, with expert advice, has suggested the PASI≥75% to be clinically meaningful and has calculated this post-hoc to use in the economic model.

Summary of comparative health economic evidence

The manufacturer's submission modelled Dovobet® once daily (OD), for four weeks as first line therapy with calcipotriol twice daily (BD) as second line therapy, compared to:

- Calcipotriol OD as first line with a potent steroid as second line
- Calcipotriol twice daily (BD) as first line with a potent steroid as second line
- A potent steroid first line and calcipotriol OD as second line.
- Calcipotriol plus a potent steroid as first and second line.

Values for the clinical effectiveness and quality of life parameters came from clinical trials. Key assumptions include that patients who fail to respond (PASI< 75) after second line topical treatments are referred, with a 6 month waiting list, for phototherapy (20 treatments of

narrowband UVB). The primary outcome measure was cost /QALY. A baseline utility of 0.80 was used, with responders gaining a 0.09 increment of utility.

The results showed that after 1 year, four weeks of Dovobet® as first line followed by calcipotriol BD as second line was cheapest and had the highest number of quality adjusted life years. This result was robust under the conducted sensitivity analyses.

The main drivers were the better clinical effectiveness rates observed from the trials, which reduced the number of patients requiring phototherapy.

Patient and public involvement

Patient Interest Group Submission: Psoriasis Scotland Arthritis Link Volunteers (PSALV)
Patient Interest Group Submission: The Psoriasis Association
Patient Interst Group Submission: Psoriatic Arthritis Liaison Scotland

Budget impact

The manufacturer provided a range of estimates from an annual saving of £113k to an additional annual cost of £52k for 2006. The higher cost uses assumptions that are consistent with the economic model.

The estimates assume 64,550 patients with chronic plaque psoriasis of whom 43,000 are being treated and an incidence rate of about 4,200.

Guidelines and protocols

The British Association of Dermatologists and Primary Care Dermatology Society have issued recommendations for the initial management of psoriasis. These list the following options with sequence of choice likely to vary according to the extent and pattern of psoriasis and patient preference. Specific reference is made to Dovobet®. Options include tar based cream, or a tar/corticosteroid mixture; moderate potency topical corticosteroid; vitamin D analogue; calcipotriol with betamethasone dipropionate as a combination product (note that long term data regarding relapse rates is not yet established); vitamin A analogue (retinoid) and dithranol preparations.

The Centre for Change and Innovation within NHS Scotland has recently produced a Psoriasis Patient Pathway (April 2005). This lists primary care options for management of chronic plaque psoriasis as: emollient; vitamin D analogue +/- topical steroid; coal tar; dithranol cream as short contact therapy and topical retinoid.

Additional information

SMC advice (No.09/02, September 2002) stated that Dovobet was not recommended for use within NHS Scotland. Given its higher costs, value for money was not demonstrated for this product. For patients who may benefit from a combination of corticosteroid and calcipotriol, it may be more appropriate to have independent control over the potency, dosing and duration of corticosteroid used than to use a fixed dose combination involving a (very) potent steroid.

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 15 September, 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

British Association of Dermatologists and Primary Care Dermatology Society. Recommendations for the initial management of psoriasis, January 2003. www.bad.org.uk

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Guenther L et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomised, double-blind, vehicle-controlled clinical trial. Br J Dermatol 2002;147(2):316-323

Kaufmann R et al. A new calcipotriol/betamethasone dipropionate (Daivobet) is an effective once daily treatment for psoriasis vulgaris. Dermatology 2002;205(4):389-393

Ortonne J.-P et al. Efficacy of treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris: A randomised, double-blind trial. Dermatology 2004;209:308-313

Kragballe K et al. Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. Br J Dermatol 2004;150:1167-1173

van der Kerhof PCM. The impact of a two-compound product containing calcipotriol and betamethasone dipropionate (Daivobet®/Dovobet®) on the quality of life in patients with psoriasis vulgaris: a randomised controlled trial. Br J Dermatol 2004; 151: 663-668.

CPMP Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02, November 2004), available at www.emea.eu.int/pdfs/human/ewp/245402en.pdf

Centre for Change and Innovation. Dermatology –Psoriasis Patient Pathway. April 2005. www.cci.scot.nhs.uk